Supreme Court, U.S.
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No. 06-1291

In the Supreme Court of the United States

AMGEN INC.,

Petitioner,

v.

HOECHST MARION ROUSSEL, INC. (now known as AVENTIS PHARMACEUTICALS INC.) and TRANSKARYOTIC THERAPIES, INC. (now known as SHIRE HUMAN GENETIC THERAPIES, INC.),

Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

PETITION FOR A WRIT OF CERTIORARI APPENDIX VOLUME II OF II

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APPENDIX D

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

01-1191, -1218

AMGEN INC.,
Plaintiff-Cross Appellant,

v.

HOECHST MARION ROUSSEL, INC.
(now known as Aventis Pharmaceuticals, Inc.)
and TRANSKARYOTIC THERAPIES, INC.,
Defendants-Appellants.

DECIDED: January 6, 2003

Before MICHEL, CLEVENGER, and SCHALL, *Circuit Judges.*

Opinion for the court filed by *Circuit Judge* MICHEL. Dissenting opinion [p. 410a, *infra*] filed by *Circuit Judge* CLEVENGER.

MICHEL, *Circuit Judge.*

Plaintiff-Cross Appellant Amgen Inc. ("Amgen") is the owner of numerous patents directed to the production of erythropoietin ("EPO"), a naturally occurring hormone that controls the formation of red blood cells in bone marrow. Amgen markets and sells EPOGEN®, a highly successful commercial embodiment of the patented erythropoietin. Seeking to impede defendants-appellants Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc. (collectively "TKT") from commercializing a competitive EPO product, Amgen filed a declaratory judgment action in the United States District Court for the District of Massachusetts in April

1997, alleging that TKT's Investigational New Drug Application ("INDA") infringed United States Patent Nos. 5,547,933 ("the '933 patent"); 5,618,698 ("the '698 patent"); and 5,621,080 ("the '080 patent"). The complaint was amended in October 1999 to include United States Patent Nos. 5,756,349 ("the '349 patent") and 5,955,422 ("the '422 patent"), which issued after suit was filed.

After a three-day *Markman* hearing, the case was tried to the court for 23 days over the course of four months. In January 2001, the district court issued an exhaustive 244-page opinion in which it: (i) construed the disputed claims; (ii) held each of the patents enforceable; (iii) held the '080, '349 (product claims), and '422 patents valid and infringed; (iv) held the '698 patent not infringed; and (v) held the '933 patent not infringed or, in the alternative, invalid for failure to satisfy 35 U.S.C. § 112. *Amgen, Inc. v. Hoescht Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 57 USPQ2d 1449 (D. Mass. 2001). On appeal, TKT urges reversal on the grounds that the patents in suit are all unenforceable, that the district court's claim construction was erroneous, and alternatively, if that claim construction was correct, that the court's validity determinations were erroneous. Amgen asserts, in its cross appeal, that the district court committed error: (i) by comparing the accused process to the examples in the specification rather than the limitations of the method claims of the '349 and '698 patents; and (ii) by holding the '933 patent invalid for failure to comply with § 112. We heard oral argument on May 7, 2002.

We commend the district court for its thorough, careful, and precise work on what is indubitably a legally difficult and technologically complex case. There is no doubt that the court marshaled tremendous time and resources in its effort to reach correct results. Nevertheless, because we must conclude that the court committed certain errors of law in certain of its validity and infringement determinations, we cannot affirm the judgment in its entirety.

We affirm *in toto* the district court's claim construction. We also affirm: (i) its determination that none of the patents in suit is unenforceable for inequitable conduct; (ii) its contingent determination that the '933 patent is invalid under § 112 ¶ 1; (iii) its grant of summary judgment of infringement of '422 patent claim 1; (iv) its determination that the '080, '933, '349, and '698 patents are not anticipated by the Sugimoto reference; and (v) its determination that '349 patent claims 1, 3-4, and 6 are infringed. Because the district court misapplied the law, however, we vacate: (i) its determination that the '933 patent is not infringed; (ii) its determination that the '080 patent is infringed under the doctrine of equivalents; (iii) its determination that the '080, '349, and '422 patents are not invalid; and (iv) its determination that the asserted method claims of the '698 patent and '349 patent claim 7 are not infringed. Accordingly, we remand for the district court to reconsider: (i) whether the '080, '349, and '422 patents are obvious in light of the Sugimoto prior art or anticipated or obvious in light of the Goldwasser prior art; (ii) whether the '422 patent is anticipated by Sugimoto reference (and whether Amgen can prove its nonenablement); (iii) whether the asserted claims of the '698 patent and '349 patent claim 7 are infringed by the accused method; and (iii) whether the '080 patent is infringed under the doctrine of equivalents. In sum, as further explained in detail below, we affirm in part, vacate in part, and remand for further proceedings consistent herewith.

BACKGROUND

As the district court set out in painstaking detail the basics of the underlying technology, we will provide only a brief summary here. The reader's familiarity with the fundamentals of molecular biology, genetics, and recombinant DNA technology necessary to this appeal is presumed.[1]

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[1] For further reading on these subjects, *see generally* Robert A.

EPO is a naturally occurring protein that initiates and controls erythropoiesis, the production of red blood cells in bone marrow. Red blood cells are critical because they contain hemoglobin, a protein responsible for transporting oxygen from the lungs to peripheral tissues. Because EPO is produced in the kidney, patients with chronic kidney (renal) failure lack normal levels of EPO and, as a result, have a sub-optimal number of red blood cells—a condition called anemia. The therapeutic goal for treating anemic patients is to increase the "hematocrit level," which represents the ratio of red blood cells to total blood volume, to normal or near-normal levels. This is accomplished through the introduction of additional EPO into the patient's system.

The implementation of this seemingly simple solution, introduction of exogenous EPO, proved to be difficult. Because human EPO is produced in very small amounts (even from the healthy human kidney), it is difficult to obtain by conventional methods. Early attempts to recover EPO from plasma or from human urine ("urinary EPO" or "uEPO") were unsuccessful because such recovery employed techniques that were complicated, yet still resulted in a low-yield, high-impurity, or unstable EPO end product. '933 patent, col. 6, line 60-col. 7, line 42. Similar attempts using antibody techniques failed because of difficulty in providing for the large-scale isolation of quantities of EPO from mammalian sources sufficient for further analysis, clinical testing, or therapeutic use. *Id.*, col. 9, lines 2-8. The first successful method of production of a therapeutically effective amount of erythropoietin used recombinant EPO ("rEPO") techniques; Amgen is recognized as the pioneer. *See, e.g.*, *Molecular Biology and Biotechnology* at 108.

Meyers, ed., *Molecular Biology and Biotechnology: A Comprehensive Desk Reference*, VCH Publishers (1995); Benjamin Lewin, *Genes VII*, Oxford Univ. Press (2000); James D. Watson et al., *Recombinant DNA* (2d ed. 1992).

Amgen scientist Dr. Fu-Kuen Lin is the named inventor on all five patents in suit. Instead of attempting to purify EPO from natural sources, Lin isolated and characterized monkey and human EPO genes, then used conventional recombinant DNA technology to produce large amounts of rEPO. '933 patent, col. 13, lines 50-53. Lin was able to determine the entire DNA sequence of human EPO and from that, its predicted amino acid sequence. *Id.*, Fig. 6; col. 10, lines 65-col. 11, line 2. Using the isolated human EPO gene, Lin described several methods for producing therapeutically effective amounts of human EPO using an expression vector.[2] *Id.*, col. 21, line 42-col. 25, line 27.

EPOGEN®, the commercial embodiment of Amgen's patented EPO product, is produced by the method disclosed in patent specification Example 10. That example describes the production of human EPO through transfection (introduction) of exogenous DNA into host Chinese hamster ovary ("CHO") cells. The CHO host cell, using its own transcription machinery, then expresses human rEPO in abundance, which then accumulates in the host cell cytoplasm or in the culture media. *Id.*, col. 37, lines 43-49. The rEPO so recovered has the same or similar amino acid sequences and biological properties as naturally occurring human EPO, but differs in its "glycosylation," *i.e.*, in the patterns of branched carbohydrate chains that attach to the protein. '933 patent, col. 10, lines 34-41.

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[2] An "expression vector" is a circular piece of DNA (or "plasmid") that is inserted into a host cell to produce (or "express") a protein. The expression vector carries the gene encoding for the protein of interest (in this case human EPO), a marker that assures that the vector is properly introduced into the host cell, and a promoter site that the host will recognize to transcribe the vector's DNA. *See generally* Thomas E. Crieghton, ed., *Encyclopedia of Molecular Biology*, vol. 2, John Wiley & Sons, Inc. (1999) at 883-86.

The patents in suit, which all claim priority to a December 1983 application long since abandoned, are continuations of a common ancestor—United States Patent No. 4,703,008—which was at issue in this court's landmark decision in *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991).[3] The '933 patent issued on August 20, 1996, containing 14 claims drawn primarily to a non-naturally occurring EPO product with certain characteristics. At issue in this lawsuit are claims 1, 2, and 9 (with the disputed claim terms here and below underscored):

> 1. A *non-naturally occurring erythropoietin glycoprotein* product having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and having *glycosylation which differs from that of human urinary erythropoietin.*
>
> 2. The *non-naturally occurring EPO glycoprotein* product according to claim 1 wherein said product has a higher molecular weight than *human urinary EPO* as measured by SDS-PAGE.
>
> 9. A pharmaceutical composition comprising an effective amount of a glycoprotein product effective for erythropoietin therapy according to claim 1, 2, 3, 4, 5, or 6 and a pharmaceutically acceptable diluent, adjuvant or carrier.

The '698 patent issued on April 8, 1997, containing nine claims drawn to a process for producing a glycosylated erythropoietin polypeptide. At issue are claims 4-9:

> 4. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase

---

[3] Because the patents in suit share an identical disclosure, all citations will be to the '933 specification unless otherwise noted.

production of reticulocytes and red blood cells comprising the steps:

a) growing, under suitable nutrient conditions, *vertebrate cells* comprising promoter DNA, other than human erythropoietin promoter DNA, *operatively linked to DNA* encoding *the mature erythropoietin amino acid sequence of* FIG. 6; and

b) isolating said glycosylated erythropoietin polypeptide expressed by said cells

5. The process of claim 4 wherein said promoter DNA is viral promoter DNA.

6. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:

a) growing, under suitable nutrient conditions, *vertebrate cells* comprising amplified *DNA encoding the mature erythropoietin amino acid sequence of FIG. 6*; and

b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.

7. The process of claim 6 wherein *said vertebrate cells* further comprise amplified marker gene DNA.

8. The process of claim 7 wherein said amplified marker gene DNA is Dihydrofolate reductase (DHFR) gene DNA.

9. The process according to claims 2, 4 and 6 wherein said cells are *mammalian cells.*

The '080 patent, which issued with seven claims on April 15, 1997, claims both an isolated erythropoietin glycoprotein and

a method for therapeutically administering a pharmaceutical composition thereof. Only product claims 2-4 are at issue:

> 2. An isolated erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises *the mature erythropoietin amino acid sequence of FIG. 6* and is not isolated from human urine.
>
> 3. A *non-naturally occurring erythropoietin glycoprotein* having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises *the mature erythropoietin amino acid sequence of FIG. 6.*
>
> 4. A pharmaceutical composition comprising a therapeutically effective amount of an erythropoietin glycoprotein product according to claim 1, 2, or 3.

The '349 patent, which issued on May 26, 1998, contains one method claim and six product claims that are drawn generally to types of vertebrate cells grown in culture. At issue are claims 1, 3-4, and 6-7:

> 1. *Vertebrate cells* which can be propagated in vitro and which are capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay, said cells comprising *non-human DNA sequences that control transcription of DNA encoding human erythropoietin.*
>
> 3. *Vertebrate cells* according to claim 1 capable of producing in excess of 1000 U erythropoietin per 10^6 cells in 48 hours.
>
> 4. *Vertebrate cells* which can be propagated in vitro which comprise *transcription control DNA sequences*,

other than human erythropoietin transcription control sequences, for production of human erythropoietin, and which upon growth in culture are capable of producing in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay

6. *Vertebrate cells* according to claim 4 capable of producing in excess of 1000 U erythropoietin per 10^6 cells in 48 hours.

7. A process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, *vertebrate cells* according to claim 1, 2, 3, 4, 5, or 6.

Last, the '422 patent, containing two claims directed to therapeutically effective pharmaceutical compositions of EPO, was granted on September 21, 1999. Only claim 1 is in dispute:

1. A pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is *purified from mammalian cells grown in culture.*

The district court conducted the *Markman* hearing in late March and early April 2000 in advance of Amgen's motion for summary judgment of infringement. The court entertained oral argument, aided by demonstrative exhibits, but heard no witness testimony and received no evidence. *Amgen*, 126 F. Supp. 2d at 81, 57 USPQ2d at 1455. At the close of the hearing, the court announced its claim constructions from the bench; these oral rulings were included and expounded upon in the written opinion ruling on the merits following trial. *Id.* at 84-94, 57 USPQ2d at 1457-64.

Immediately following the *Markman* hearing, the court turned to Amgen's pending motion for summary judgment of

infringement of '422 patent claim 1 and '349 patent claims 1, 3-4, and 6. As to the '422 patent, the district court found: (1) that it was uncontradicted that the accused product, HMR4396, was a pharmaceutical composition; (2) that it necessarily contained a therapeutically effective amount of human erythropoietin (otherwise, the filing of an INDA would be pointless); and (3) that the record evidence demonstrated that HMR4396 contained a pharmaceutically acceptable diluent, adjuvant, or carrier as claimed in claim 1. *Id.* at 94-95, 57 USPQ2d at 1455-56. The sole remaining question was whether the accused erythropoietin product had been "purified from mammalian cells grown in culture." The court found, in light of its claim construction that the term "mammalian" comprises human cells, that the last limitation had been met. *Id.* at 95-96, 57 USPQ2d at 1466. The court therefore granted summary judgment of infringement of '422 patent claim 1.

Trial commenced on May 15, 2000. When Amgen rested at the close of its infringement case, the court granted TKT's motions for judgment of non-infringement of the '698 patent and literal non-infringement of the '080 patent. *Id.* at 99-104, 57 USPQ2d at 1469-73. At the close of TKT's rebuttal case, the court granted Amgen's motion for judgment of validity, finding that TKT had not carried its burden of clearly and convincingly proving anticipation or obviousness. *Id.* at 104-17, 57 USPQ2d at 1473-82. The remaining issues were taken under advisement. The court's opinion issued on January 19, 2001, and these timely cross-appeals followed. Vested with jurisdiction under 28 U.S.C. § 1295(a)(1), we address below the myriad issues before us.

DISCUSSION

I

The rules are by now well known. Because claim language defines claim scope, the first step in an infringement analysis

is to construe the claims, *i.e.*, to determine the scope and meaning of that which is allegedly infringed. *Markman v. Westview Instr., Inc.*, 52 F.3d 967, 976, 34 USPQ2d 1321, 1326 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370, 38 USPQ2d 1461 (1996). To properly construe the claims, a court must examine the claims, the rest of the specification, and, if in evidence, the prosecution history. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582, 39 USPQ2d 1573, 1576-77 (Fed. Cir. 1996). Thereafter, the properly construed claims are compared to the accused product or process to determine whether each of the claim limitations is met, either literally or equivalently. *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1365, 62 USPQ2d 1658, 1662 (Fed. Cir. 2002).

There are two general areas of dispute TKT raises regarding the district court's claim construction. First, TKT urges that the court erred by failing to limit the asserted claims to exogenous DNA, despite the fact that none of the claims in suit contain an "exogenous DNA" limitation. Second, TKT asserts that the court erred by refusing to limit the terms "vertebrate," "mammalian," and "non-naturally occurring"—each of which appear in varying degrees within the asserted claims—such that they exclude host human cells which, of course, are used by the accused infringers. We consider the trial court's claim construction—a matter of law—afresh on appellate review. See *Cybor Corp. v. FAS Tech., Inc.*, 138 F.3d 1448, 1455, 46 USPQ2d 1169, 1173 (Fed. Cir. 1998) (en banc).

A

We turn first to address a threshold definitional dispute that carries with it important consequences for the infringement issues decided by the district court and facing us on appeal, to wit, what is the distinction between exogenous, as opposed to endogenous, DNA in recombinant DNA parlance? According to TKT, it practices an innovative process using homologous

recombination: it takes the ordinarily unexpressed endogenous (or "native") EPO gene in human cells and transfects "a viral promoter and certain other DNA" that does not encode EPO. That "other" DNA is inserted into the chromosome at a pre-determined, targeted location upstream from the endogenous EPO gene to produce what TKT has termed "Gene-Activated EPO," or "GA-EPO." TKT contrasts this method with that of Amgen, which TKT asserts undeniably uses exogenous DNA.

None of the asserted claims contain either an "exogenous DNA" or "endogenous DNA" limitation.[4] Based upon representations allegedly made by Amgen during the prosecution of the patents in suit, however, TKT argues that many of the claims the district court construed should have been defined narrowly to include only exogenous DNA. The district court rejected this argument, as do we.

"It is the claims that measure the invention." *SRI Int'l v. Matsushita Elec. Corp.*, 775 F.2d 1107, 1121, 227 USPQ 577, 585 (Fed. Cir. 1985) (*en banc*). Because the claims are best understood in light of the specification of which they are a part, however, courts must take extreme care when ascertaining the proper scope of the claims, lest they simultaneously import into the claims limitations that were unintended by the patentee. *See, e.g., Hoganas AB v. Dresser Indus., Inc.*, 9 F.3d 948, 950, 28 USPQ2d 1936, 1938 (Fed. Cir. 1993) ("It is improper for a court to add extraneous limitations to a claim, that is limitations added wholly apart from any need to interpret what the patentee meant by particular words or phrases in the claim." (citation omitted)).

---

[4] That is not to say that there are no claims that have such a limitation. Unasserted claim 3 of the '933 patent, for example, does contain such a limitation: "A non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin . . . ." col. 38, lines 26-29.

The danger of improperly importing a limitation is even greater when the purported limitation is based upon a term not appearing in the claim. "If we once begin to include elements not mentioned in the claim in order to limit such claim . . ., we should never know where to stop." *Johnson Worldwide Assocs., Inc. v. Zebco Corp.*, 175 F.3d 985, 990, 50 USPQ2d 1607, 1610 (Fed. Cir. 1999) (quoting *McCarty v. Lehigh Val. R.R.*, 160 U.S. 110, 116 (1895)).

Amgen's inventive EPO product, according to the disclosure in the '933 patent, is "uniquely characterized by being the product of prokaryotic or eucaryotic host expression (e.g., by bacteria, yeast and mammalian cells in culture) of exogenous DNA sequences obtained by genomic or cDNA cloning or by gene synthesis." '933 patent, col. 10, lines 15-20. In discussing United States Patent No. 4,237,224 (issued to Cohen), the '933 patent defines "exogenous DNA" by reference as DNA that is foreign to the host organism. *See id.* col. 2, lines 41-47 ("[T]he Cohen et al. patent first involve[s] manufacture of a transformation vector by enzymatically cleaving viral or circular plasmid DNA to form linear DNA strands. Selected foreign ('exogenous' or 'heterologous') DNA strands usually including sequences coding for desired product are prepared in linear form through use of similar enzymes."). During the prosecution of Serial No. 08/468,369, which became the '349 patent, the examiner commented that the application "teaches and enables only cells that have been transformed with exogenous DNA that encodes erythropoietin (EPO) that have the high EPO production required by the claims." TKT asserts, as a result, that its GA-EPO product and process fall outside the scope of the asserted claims because Amgen repeatedly has characterized its claimed products and processes as requiring the use of exogenous EPO DNA, and hence the claims should be limited thereto.

Guided by our principles of claim construction, we agree with the district court that TKT improperly seeks to import

the "exogenous" limitation into the claims. The plain meaning of the claims controls here, and they plainly are not so limited. The statement that the invention is "uniquely characterized" by the expression of exogenous DNA sequences does not impel us to accept TKT's position when the asserted claims do not contain such an express limitation. In fact, TKT's position is undermined by the doctrine of claim differentiation, as reference to other claims clearly indicates that Amgen did not intend to limit the invention to the use of exogenous DNA. Unasserted claim 3 of the '933 patent, for example, is virtually identical to claim 1, save for the express limitation regarding the use of "exogenous DNA" (underlined portioned indicating differences).

Claim 1	Claim 3
A non-naturally occurring *erythropoietin* glycoprotein product *having* the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and having glycosylation which differs from that of human urinary erythropoietin.	A non-naturally occurring glycoprotein product *of the expression in a mammalian host cells of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin said product possessing* the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and having glycosylation which differs from that of huma urinary erythropoietin.

Our court has made clear that when a patent claim "does not contain a certain limitation and another claim does, that limitation cannot be read into the former claim in determining either validity or infringement." *SRI Int'l*, 775 F.2d at 1122, 227 USPQ at 586; *see also O.I. Corp. v. Tekmar Co., Inc.*, 115 F.3d 1576, 1582, 42 USPQ2d 1777, 1781 (Fed. Cir.

1997) (expressing the notion that there are practical limits to the doctrine of claim differentiation: "the doctrine cannot alter a definition that is otherwise clear from the claim language, description, and prosecution history."). There is a rebuttable presumption that different claims are of different scope. *See Kraft Foods, Inc. v. Int'l Trading Co.*, 203 F.3d 1362, 1366-67, 53 USPQ2d 1814, 1817 (Fed. Cir. 2000); *Multiform Dessicants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1479-80, 45 USPQ2d 1429, 1434 (Fed. Cir. 1998).

The examiner's statement in the prosecution history gives us no pause, as the basis for his rejection was not because transformation with exogenous DNA was not taught, but because "the high EPO production required by the claims" was not. *See* J.A. at 1302 ("The instant application does not guide one of ordinary skill in the art in the discovery of non-transformed vertebrate cells that are capable of the high EPO production recited in the instant claims, [as demonstrated in the reference,] each of which discloses levels of EPO production by vertebrate cells in culture that are far below those levels required in the instant claims."). TKT's position is further undermined because the asserted claims issued. We must presume the examiner did his job, and if he truly thought that the specification taught or enabled only the use of exogenous DNA, the asserted claims would not have issued.

In the end, TKT has not directed our attention to anything in the intrinsic record that rebuts the presumption that the plain meaning of the terms controls. Accordingly, we conclude that the scope of the asserted claims should not be limited to the expression of exogenous DNA.

B

TKT asserts, in addition to the exogenous/endogenous distinction discussed above, that the district court misconstrued the terms "non-naturally occurring," "vertebrate cells,"

and "mammalian cells"—which appear in many of the asserted claims—to include human cells. Reviving the same argument the district court rejected below, TKT contends Amgen expressly disavowed the use of human cells to make human EPO.

The district court found that the definition of the term "non-naturally occurring" can be discerned through the doctrine of claim differentiation. Specifically, the court concluded that TKT's proffered construction must fail in light of '933 patent claim 3, discussed previously, which claims a "*non-naturally occurring* glycoprotein product of the expression in a *mammalian* host cell of an exogenous DNA sequence encoding *human* erythropoietin . . . ." By its terms, then, this claim would cover the expression of human DNA in a cat host cell, for example, because a cat is a mammal. The court thus concluded that the phrase "non-naturally occurring" would be redundant in claim 3 if the phrase had the meaning TKT sought to ascribe to it. Further, because the patent specification compares the biological activity of synthetic products to "EPO isolates from natural sources" or "natural EPO isolates," the court concluded that non-naturally occurring simply means "not occurring in nature." *Amgen*, 126 F. Supp. 2d at 90-91, 57 USPQ2d at 1462-63.

Similarly, finding that the term vertebrate is widely known and understood to cover anything with "a segmented bony or cartilaginous spinal cord [which obviously includes humans]," *id.* at 85, 57 USPQ2d at 1457-58, the court adopted Amgen's proposed construction. The court also adopted Amgen's proposed construction of the term "mammalian cells" appearing in '422 patent claim 1 and '698 patent claim 9 under a similar rationale. *Id.* at 84-86, 57 USPQ2d at 1458.

We indulge a heavy presumption that a claim term carries its ordinary and customary meaning. *CCS Fitness*, 288 F.3d at 1366, 62 USPQ2d at 1662; *see also Gart v. Logitech, Inc.*,

254 F.3d 1334, 1341, 59 USPQ2d 1290, 1295 (Fed. Cir. 2001). Although TKT is correct that the prosecution history is always relevant to claim construction, it is also true that the prosecution history may not be used to infer the intentional narrowing of a claim absent the applicant's clear disavowal of claim coverage, such as an amendment to overcome a rejection. *See York Prods., Inc. v. Central Tractor & Farm Fam. Ctr.*, 99 F.3d 1568, 1575, 40 USPQ2d 1619, 1624 (Fed. Cir. 1996). No such clear disavowal occurred here.

We agree with Amgen that the specification expressly describes humans as a subset of mammals, and mammals, in turn, as a subset of vertebrates. *See* '933 patent, col. 4, lines 47-48; col. 10, line 21. Moreover, the specification can fairly be read to, if not expressly, disclose the use of human DNA in human host cells in culture:

> Conspicuously comprehended are expression systems involving vectors of homogeneous origins applied to a variety of bacterial, yeast, and mammalian cells in culture as well as to expression systems not involving vectors . . . . *In this regard, it will be understood that expression of, e.g., monkey origin DNA in monkey host cells in culture and human host cells in culture, actually constitute instances of 'exogenous' DNA expression inasmuch as the EPO DNA whose high level expression is sought would not have its origins in the genome of the host.*

'933 patent, col. 37, lines 33-43 (emphasis added). The astute reader will observe what appears to be a breakdown in the parallelism of the sentence emphasized in the block quote above. Specifically, the reference to the expression of "monkey origin DNA in monkey host cells in culture and human host cells in culture" seems a bit nonsensical because the expression of monkey origin DNA in human host cells is perforce the expression of exogenous DNA. The original 1983 application from which all the patents in suit claim

priority, by contrast, contained language that upholds the parallelism of the sentence and logically makes sense. It read, in pertinent part: "[I]t will be understood that expression of, e.g., monkey origin DNA in monkey host cells in culture and *human DNA in* human host cells in culture constitute instances of 'exogenous' DNA expression." J.A. at 2862 (emphasis added).

TKT boldly asserts that the variance between the original application and the patents in suit bespeaks some volitional act by Amgen to narrow the scope of the asserted claims in light of certain experimental data. In particular, TKT advances a theory whereby Amgen intentionally removed the language from subsequent applications (allegedly) because test results using human cells were not good, and later admitted (during an opposition proceeding against the European counterpart patent) that the omission was not inadvertent. But the record contains a more benign explanation as to what happened. According to the testimony of Dr. Lin, he was unaware of, and therefore did not authorize, the change. Further, the prosecuting attorney testified in his deposition that to the best of his knowledge the error was a typographical error.

But even assuming that the error was intentional, the district court's claim construction would not be foreclosed: our precedent is clear that claims are not perforce limited to the embodiments disclosed in the specification. *E.g.*, *Rexnord Corp. v. Laitram Corp.*, 274 F.3d 1336, 1344, 60 USPQ2d 1851, 1856 (Fed. Cir. 2001) ("[A]n applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention."). Here, the patent plainly discloses the use of human host cells in culture, and our review of the record indicates no "clear disavowal" sufficient to undercut the express disclosure in the specification.

As a result, we are satisfied that the terms "non-naturally occurring," "vertebrate," and "mammalian" should be construed as they were by the district court, in a manner consistent with their plain meaning. Accordingly, we reject TKT's attempt to limit the scope of the asserted claims under an unduly constricted reading of the specification.

C

The final claim construction issue TKT raises is aimed at the district court's alleged failure to discern "source and process" limitations in claims of the '080, '349, and '422 patents. According to TKT, the trial court erred by concluding that the asserted claims are product claims, i.e., that they are directed to a structural entity that is not defined or limited by how it is made. TKT summarily states that this holding must be erroneous because, it asserts, the patentability of the claims depended on the process since "Amgen tried, but failed, to distinguish rEPO from prior art EPOs based on physical differences." We do not agree.

It is telling that neither in the briefing nor at oral argument did TKT direct us to any specific statement in the prosecution history to support the contention that the patentability of the product claims in suit depended upon the process by which those products are obtained. In fact, the original claims of at least one of the patents (the '080 patent) were drafted as product-by-process claims, which claims were cancelled and replaced with "pure" product claims. This is strong evidence that both the patentee and the examiner viewed the claims that ultimately issued as lacking a process component. *See Vanguard Prods., Inc. v. Parker Hannifin Corp.*, 234 F.3d 1370, 1372, 57 USPQ2d 1087, 1089 (Fed. Cir. 2000) ("Parker Hannifin argues that the prosecution history shows that the Vanguard inventors viewed co-extrusion as 'fundamental' to manufacture of the claimed gasket, thereby imposing this process of manufacture upon the product claims . . . . However, review of the prosecution history shows that during

examination the examiner as well as the applicant treated the product claims as directed to the product itself, and examined the application accordingly.").

In any event, we are not convinced that the source limitations in the asserted claims convert the claims into anything other than product claims. As to the '080 patent, the "non-naturally occurring" limitation in claims 3 and 4 merely prevents Amgen from claiming the human EPO produced in the natural course. By limiting its claims in this way Amgen simply avoids claiming specific subject matter that would be unpatentable under § 101. This court has endorsed this approach, recognizing that patentees can use *negative* limitations such as "non-human" and "non-natural" to avoid rejection under § 101. See *Animal Legal Def. Fund v. Quigg*, 932 F.2d 920, 923, 18 USPQ2d 1677, 1680 (Fed. Cir. 1991). The district court arrived at a similar conclusion, *Amgen*, 126 F. Supp. 2d at 89, 57 USPQ2d at 1462-63, and TKT has not demonstrated any error in that conclusion. Similarly, the "not isolated from human urine" limitation in claims 2 and 4 of the '080 patent simply requires that the claimed EPO, however made, be obtained from a source other than human urine. Each of these limitations only excludes human EPO from specific sources and does not restrict the claimed EPO to that produced from any particular source or by any particular method. In sum, claims 2, 3, and 4 of the '080 patent remain broadly drawn to the described "erythropoietin glycoprotein" or "pharmaceutical composition" produced by any method, or obtained from any source, other than those specifically excluded.

As to the '422 patent, the limitation "purified from mammalian cells grown in culture" in claim 1 clearly limits the source of the EPO used in the claimed "pharmaceutical composition." The limitation only speaks to the source of the EPO and does not limit the process by which the EPO is expressed. Rather, the claim is broadly drawn to a "pharma-

ceutical composition" having certain elements, one of those being EPO "purified from mammalian cells in culture." This reading is in line with the district court's construction and, again, TKT directs us to no error.[5]

II

It is axiomatic that claims are construed the same way for both invalidity and infringement. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 842 F.2d 1275, 1279, 6 USPQ2d 1277, 1280 (Fed. Cir. 1988). But because the features of the accused product or process are often undisputed, this axiom invites a common approach in the appellate arguments by accused infringers: the principal argument challenges the correctness of a trial court's broad claim construction; the contingent argument, assuming the trial court's claim construction is affirmed, challenges validity under 35 U.S.C. § 112 ¶ 1 of the asserted patents in light of that broad construction. *See, e.g., Adv. Cardiovascular Sys. v. Medtronic, Inc.*, 265 F.3d 1294, 60 USPQ2d 1161 (Fed. Cir. 2001); *PPG Indus. v. Guardian Indus. Corp.*, 75 F.3d 1558, 37 USPQ2d 1618 (Fed. Cir. 1996); *Kalman v. Kimberly-Clark Corp.*, 713 F.2d 760, 218 USPQ 781 (Fed. Cir. 1983). TKT employs that approach here. We therefore think it appropriate to address the relevant § 112 issues before turning to the issue of infringement.

Section 112 of the patent statute describes what must be contained in the patent specification. Among other things, it must contain "a written description of the invention, and of the manner and process of making and using it . . . [such] as to enable any person of ordinary skill in the art to which it pertains . . . to make and use the same . . . ." 35 U.S.C. § 112 ¶ 1. Thus, this statutory language mandates satisfaction of two separate and independent requirements: an applicant

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[5] We do not hold that these limitations lack meaning, only that they mean just what they say. Accordingly, they limit only the source from which the EPO is obtained, not the method by which it is produced.

must both describe the claimed invention adequately and enable its reproduction and use. *See Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Third, though not in issue here, he must disclose what he considers the best mode of practicing his invention.

A

The purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not; the applicant for a patent is therefore required to "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." *Id.* at 1561, 19 USPQ2d at 1115 (citation omitted). Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan. *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997) ("The description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). "Compliance with the written description requirement is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" *Enzo Biochem v. Gen-Probe, Inc.*, 296 F.3d 1316, 1324, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002) (citation omitted). Because of its fact intensive nature, we review a district court's decision on the adequacy of written description for clear error. *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000) (citations omitted).

In addressing TKT's written description arguments, the district court carefully examined whether Amgen's specification adequately described the full breadth of the claims. In the end, the district court rejected TKT's written description challenge, finding that TKT had proven its case only by a preponderance of the evidence—*not* the clear and convincing standard required as a matter of law. Acknowledging the

presence of "a genuine dispute between the expert witnesses," the court weighed the testimony and found that the evidence showed that the descriptions adequately described to those of ordinary skill in the art in 1984 the use of the broad class of available mammalian and vertebrate cells to produce the claimed high levels of human EPO in culture. *Amgen*, 126 F. Supp. 2d at 149, 57 USPQ2d at 1507. In so doing, the court credited in particular the testimony of Amgen's expert, Dr. Harvey Lodish, who testified, among other things, that there might be "minor differences" in applying the method of the disclosed examples (utilizing CHO and COS-1 (monkey) cells) to any vertebrate or mammalian cells, but that those of ordinary skill could "easily" figure out those differences in methodology. *Id.*, 57 USPQ2d at 1507.

Much of TKT's argument on appeal challenging this finding dovetails with its claim construction arguments we have already found lacking. For example, TKT asserts that the Amgen patents do not satisfy the written description requirement because: (1) Amgen failed to sufficiently describe the use of all vertebrate and mammalian cells; (2) Amgen deleted use of exogenous human EPO DNA in human cells from its applications;[6] (3) Amgen expressly excluded the use of endogenous EPO DNA; (4) Amgen emphasized that the advantage of its invention was "freedom from association with human proteins"; and (5) in using the "uniquely characterized" language to describe the polypeptides of the invention, Amgen identified exogenous EPO DNA as an essential element of the invention. As a result of these shortcomings, argues TKT, it has clearly and convincingly proven invalidity under *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997), *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473,

[6] We addressed this point in our claim construction analysis on pages 17-18 *ante*, finding that the written description did not exclude human cells from the scope of the claims. That analysis suffices here as well.

45 USPQ2d 1498 (Fed. Cir. 1998), and *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). We are not persuaded that these precedents mandate reversal of the trial court's factual findings as clearly erroneous regarding the written descriptions.

First, in addressing the adequacy of the written description of the '422 patent and with respect to TKT's exogenous DNA arguments, the district court noted:

> When the claim is to a composition rather than a process, the written description requirement does not demand that the specification describe technological developments in the way in which the claimed composition is made that may arise after the patent application is filed. *See United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1251 [9 USPQ2d 1461, 1465] (Fed. Cir. 1989); *In re Koller*, 613 F.2d 819, 824-25 [204 USPQ 702, 707] (Fed. Cir. 1980); *see also In re Hogan*, 559 F.2d 595, 606 [194 USPQ 527, 538] (C.C.P.A. 1977). Instead, section 112 only requires the Court to determine whether the specification conveys to one of ordinary skill in the art as of 1984 that Dr. Lin invented the subject matter claimed in the patents-in-suit. *Reiffin*, 214 F.3d at 1346 [*Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1346, 54 USPQ2d 1915, 1917 (Fed. Cir. 2000)]. The written description inquiry, therefore, focuses on a comparison between the specification and the invention referenced by the terms of the claim—not comparison between how the product was made as disclosed in the patent and future developments of this process that might alter or even improve how the same product is made.

Amgen, 126 F. Supp. 2d at 150, 57 USPQ2d at 1508; *see also id.* at 152, 57 USPQ2d at 1509 (discussing the '080 patent), 154 n.51, 57 USPQ2d at 1510 (discussing the '349 patent). The district court therefore considered TKT's exogenous

DNA arguments and, for the reasons stated above, rejected them. On appeal TKT has not argued that its legal analysis was erroneous. Because we have not been directed to any case law to the contrary, we conclude the district court's legal conclusion based on *Phillips Petroleum* was not erroneous and that it properly handled the exogenous DNA issue.

We move now to TKT's argument that Amgen failed to sufficiently describe all vertebrate and mammalian cells as engineered in the claimed invention. We held in *Eli Lilly* that the adequate description of claimed DNA requires a precise definition of the DNA sequence itself—not merely a recitation of its function or a reference to a potential method for isolating it. 119 F.3d at 1566-67, 43 USPQ2d at 1406 (holding the disclosure of the cDNA sequence of the insulin gene of a rat did not adequately describe the cDNA sequence of the insulin gene of every vertebrate). More recently, in *Enzo Biochem*, we clarified that *Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure. *See Enzo Biochem*, 296 F.3d at 1324, 63 USPQ2d at 1613. Both *Eli Lilly* and *Enzo Biochem* are inapposite to this case because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend.[7] Instead, the claims of Amgen's patents refer to types of cells that can be used to produce recombinant human EPO. Thus, TKT can only challenge the adequacy of disclosure of the vertebrate or mammalian host cell—not the human DNA itself. This difference alone sufficiently distinguishes *Eli Lilly*, because

[7] Indeed, Amgen's patents appear to satisfy the sequence requirement in *Eli Lilly* insofar as Figure 6 of the patents expressly discloses the complete (albeit slightly incorrect) sequence of human genomic EPO DNA and the encoded DNA.

when used, as here, merely to identify types of cells (instead of undescribed, previously unknown DNA sequences), the words "vertebrate" and "mammalian" readily "convey[] distinguishing information concerning [their] identity" such that one of ordinary skill in the art could "visualize or recognize the identity of the members of the genus." *Eli Lilly*, 119 F.3d at 1567, 1568, 43 USPQ2d at 1406.[8] Indeed, the district court's reasoned conclusion that the specification's description of producing the claimed EPO in two species of vertebrate or mammalian cells adequately supports claims covering EPO made using the genus vertebrate or mammalian cells, renders *Eli Lilly* listless in this case. *Amgen*, 126 F. Supp. 2d at 149, 57 USPQ2d at 1507.

TKT's remaining arguments rely on *Gentry Gallery*. However, we see *Gentry Gallery* as similarly inapt. TKT would have us view *Gentry* as a watershed case, in reliance on an isolated statement—probably only dicta—that one of ordinary skill in the art would clearly understand that the location of the reclining controls on the claimed sectional sofa "was not only important, but essential to [the] invention." 134 F.3d at 1480, 45 USPQ2d at 1503. But as we recently indicated in *Cooper Cameron Corp. v. Kvaerner Oilfield Prods., Inc.*, 291 F.3d 1317, 1323, 62 USPQ2d 1846, 1850-51 (Fed. Cir. 2002), "we did not announce [in *Gentry*] a new 'essential element' test mandating an inquiry into what an inventor considers to be essential to his invention and requiring that the claims incorporate those elements." *See also Vas-Cath,* 935 F.2d at 1565, 19 USPQ2d at 1114; *cf. Aro Mfg. Co. v. Convertible Top Replacement Co.*, 365 U.S. 336, 345 (1961) ("[T]here is no legally recognizable or protected

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[8] There is no issue here as to *in haec verba* description because, as stated in the body of the opinion, in contrast to "cDNA"—that clearly does not describe the actual sequence of the cDNA—the words "mammalian cells" and "vertebrate cells" convey exactly what they are. Thus, this aspect of the holding in *Eli Lilly* is also inapplicable here.

'essential element,' 'gist' or 'heart' of the invention in a combination patent."). Understood in this light, one sees the holding in *Gentry* for what it really was: an application of the settled principle that a broadly drafted claim must be fully supported by the written description and drawings. *See Cooper Cameron*, 291 F.3d at 1323, 62 USPQ2d at 1850-51. After considering extensive testimony from both parties, the district court held this principle met and TKT failed to demonstrate that this analysis was clearly erroneous factually or based on an error of law. *Amgen*, 126 F. Supp. 2d at 149-50, 57 USPQ2d at 1507-08.

To the extent the particular facts of *Gentry* are relevant, we also find it distinguishable. First, there is a fundamental difference between Amgen's patented invention and the invention in *Gentry*. In *Gentry* the invention *was* the placement of reclining controls on a central console on a unit of a sectional sofa so as to allow the sofa to have two independent reclining seats face in the same direction (solving a problem present in the prior art). 134 F.3d at 1475, 45 USPQ2d at 1499. The undisclosed element leading to the *Gentry* court's holding of invalidity for lack of an adequate description was a location for the controls other than on the console—leading to a different and undescribed *product. See id.* at 1479, 45 USPQ2d at 1502-03. Amgen's invention is not the location of the control sequences and EPO DNA in relation to the cell, but rather the production of human EPO using those sequences. Thus, the undisclosed element TKT urges invalidates Amgen's product claims is a different *method* (endogenous activation) of making the claimed compositions. But, as the district court noted, under our precedent the patentee need only describe the invention as claimed, and need not describe an unclaimed method of making the claimed product. *Amgen*, 126 F. Supp. 2d at 150, 57 USPQ2d at 1507 (citing *Phillips Petroleum*, 865 F.2d at 1251, 9 USPQ2d at 1465; *In re Koller*, 613 F.2d at 824-25, 204 USPQ at 707); *see also Vas-Cath*, 935 F.2d at 1563-64, 19 USPQ2d at 1117.

This factual difference alone is sufficient to distinguish this case from *Gentry*.

Second, the statements by the patentee in the written description in this case fall short of what *Gentry* prohibits. The court in *Gentry* concluded that the inventor had clearly expressed in the written description that he considered his invention to be limited to the specific location of the controls on the console on the sofa ("the only possible location") and that any variation was "outside the stated purpose of the invention." *Gentry Gallery*, 134 F.3d at 1479, 45 USPQ2d at 1503. Indeed, in *Gentry* the inventor testified that he only considered locating the controls outside of the console—and only broadened his application claims accordingly—after seeing Gentry's competitors introduce products with controls located off the console. *Id.* Here, to be sure, Amgen made statements that its invention is "uniquely characterized" by exogenous expression of DNA. '933 patent col. 10, lines 15-20. When considered in context, however, these statements do not lead to the same conclusion as in *Gentry*. Amgen's statements simply do not clearly indicate that exogenous expression is the *only* possible mode of the invention or that other methods were outside the stated purpose of the invention. Instead, Amgen begins the background section of its written description by stating "[t]he present invention relates generally to the manipulation of genetic materials and, more particularly, to recombinant procedures making possible the production of polypeptides possessing part or all of the primary structural conformation and/or one or more of the biological properties of naturally occurring erythropoietin." '933 Patent, col. 1, lines 18-23. Because of this lack of clear statements by the patentee limiting the claimed invention (and in light of the case law discussed, *ante*), we cannot invalidate a patent for failure to describe a method of producing the claimed compositions that is not itself claimed. Nor could the patentee have described the other method, as it was not developed until 10 years later. We see *Gentry Gallery* as in-

applicable in this regard. In light of the evidentiary record and TKT's inability to persuade us that precedent requires a contrary result, we hold that the district court's finding that Amgen satisfied the written description requirement is not clearly erroneous.

B

The enablement requirement is often more indulgent than the written description requirement. The specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without "undue experimentation." *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). Before the district court, TKT bore the burden of clearly and convincingly proving facts showing that the claims were not enabled. *E.g.*, *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1375, 52 USPQ2d 1129, 1141 (Fed. Cir. 1999). Enablement is a question of law; we therefore review the trial court's determination *de novo*, deferring to its assessment of subsidiary facts underlying the legal question unless clearly erroneous. *Bruning v. Hirose*, 161 F.3d 681, 686, 48 USPQ2d 1934, 1939 (Fed. Cir. 1998).

TKT contends that the asserted claims are invalid for lack of enablement. Taking a position that virtually mirrors the written description (and claim construction) arguments previously rejected, TKT posits that the specifications do not enable an ordinarily skilled artisan to practice the full scope of the asserted claims without undue experimentation because they fail to describe the production of EPO using human cells or endogenous human EPO DNA. At bottom, TKT complains

that the court erred by failing to follow its findings to their logical conclusion.[9]

But the district court made thorough and complete factual findings supporting its holding that the claims were not proven not enabled, expressly incorporating many of its factual determinations made with respect to written description. As to TKT's endogenous/exogenous arguments, the court concluded the arguments were inapplicable as a matter of law for two reasons. First, "where the method is immaterial to the claim, the enablement inquiry simply does not require the specification to describe technological developments concerning the method by which a patented composition is made that may arise after the patent application is filed." *Amgen*, 126 F. Supp. 2d at 160, 57 USPQ2d at 1515 (citing *Phillips Petroleum*, 865 F.2d at 1251, 9 USPQ2d at 1465; *In re Koller*, 613 F.2d at 824-25, 204 USPQ at 707; *In re Hogan*, 559 F.2d at 606, 194 USPQ at 538); *see also id.* at 161, 57 USPQ2d at 1516 (discussing the '080 patent), 163-64, 57 USPQ2d at 1518 (discussing the '349 patent). Thus, the specification's failure to disclose the later-developed endogenous activation technology cannot invalidate the patent. *Id.* at 160, 57 USPQ2d at 1516. Second, "the law makes clear that the specification need teach only one mode of making and using a claimed composition." *Id.* at 160, 57 USPQ2d at 1515 (citing Johns *Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1361, 47 USPQ2d 1705, 1719 (Fed. Cir. 1998); *Engel Indus. Inc. v. Lockformer Co.*, 946 F.2d 1528, 1533, 20 USPQ2d 1300, 1304 (Fed. Cir. 1991)); *see also Durel Corp.*

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[9] TKT refers here to the district court's statement that "it appears that Dr. Lin claimed far more than he delivered." *Amgen*, 126 F. Supp. 2d at 158, 57 USPQ2d at 1514. Although this statement does seem out of kilter with the court's ultimate holding, we understand it in light of how close the court viewed the issue: "After much reflection, the court finds that Amgen survives [the enablement challenge], albeit barely." *Id.* at 157, 57 USPQ2d at 1513.

v. Osram Sylvania Inc., 256 F.3d 1298, 1308, 59 USPQ2d 1238, 1244 (Fed. Cir. 2001). This conclusion again makes the specification's failure to disclose TKT's endogenous activation technology legally irrelevant. *Amgen*, 126 F. Supp. 2d at 160, 57 USPQ2d at 1515. We reach the same conclusion on appeal, as TKT has not persuaded us that the district court's conclusions in this regard were erroneous.

Focusing specifically on the '422 patent, the enablement inquiry is whether Amgen has enabled all pharmaceutical compositions comprising "a therapeutically effective amount of human erythropoietin," "a pharmaceutically acceptable diluent, adjuvant or carrier," and human erythropoietin "purified from mammalian cells grown in culture." The court found that the specification described and enabled various possible diluents and carriers and provided specific information on effective dosages and therapeutic effect in mice. *Id.* at 148, 57 USPQ2d at 1506. Amgen also described and enabled at least one way of obtaining EPO purified from mammalian cells in culture: the genetic manipulation of CHO and COS-1 cells, followed by both described and other well known purification techniques. Finally, the court accepted testimony indicating that an ordinarily skilled artisan would infer from the COS-1 (monkey) and CHO cell examples that similar outcomes could be expected from other mammalian cells since all mammalian cells produce and secrete hormones like EPO by means of the same fundamental processes. *Id.* at 159, 57 USPQ2d at 1514-15. These are all findings of fact and they have not been shown to be clearly erroneous.

As to the '080 patent, the inquiry is whether Amgen has enabled the production of all EPO glycoproteins having "the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells," "the mature erythropoietin amino acid sequence of FIG. 6," and "[are] not isolated from human urine" or "non-naturally occurring." The court noted that Amgen disclosed the *in vivo*

biological effect of EPO upon hematocrit levels in mice and adequately disclosed the sequence of the amino acid residues in figure 6. *Id.* at 151, 57 USPQ2d at 1508-09. Amgen also described and enabled at least one method of producing EPO that was both "non-naturally occurring" and "not isolated from human urine": the genetic manipulation of CHO and COS-1 cells. The court noted with particularity that even TKT's witness, Dr. Kingston, agreed that if one of ordinary skill in the art followed the teachings of Example 10, then such a person could successfully practice the claimed invention. *Id.* at 161, 57 USPQ2d at 1516.

We address the product claims of the '349 patent in more detail, as they differ slightly from the patents we discussed above. The '349 patent claims genetically manipulated "vertebrate cells"—a composition—having certain characteristics and properties, including an ability to produce the claimed levels of human EPO.[10] The enablement question thus posed is this: having disclosed one way to make the claimed EPO-producing cell, is Amgen entitled to claim all such cells that "can be propagated *in vitro*," comprise "non-human DNA sequences that control transcription," transcribe "DNA encoding human erythropoietin," and produce the claimed amount of EPO? While our precedent does hold that disclosure of one or two species *may* not enable a broad genus, *e.g.*, *In re Vaeck*, 947 F.2d at 495-96, 20 USPQ2d at 1444-45, the district court made several fact-findings indicating that any gaps between the disclosures and the claim

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[10] Following the dissent's "machine" analogy, the "machine" is a genetically altered vertebrate cell containing transcription control sequences used to transcribe a human EPO gene to express the claimed levels of human EPO. Simply altering the way the human EPO gene is inserted or activated—whether it be through transformation with exogenous DNA or through activation of an endogenous gene—does not make this a different "machine" once built; rather, it only changes the way it was "constructed."

breadth could be easily bridged. *See, e.g.*, *Amgen*, 126 F. Supp. 2d at 149, 57 USPQ2d at 1514 (crediting Amgen's expert Dr. Lodish's statement that "one of ordinary skill in the art, me, my students, would have understood this not to be limited to the specific types of cells that were used in this example, that other vertebrate cells, mammalian cells, could have been used"); *cf. Enzo Biochem*, 188 F.3d at 1367-68, 1372, 52 USPQ2d at 1133, 1136-37 (affirming nonenablement of claims to anti-sense DNA technology applied to all eukaryotic and prokaryotic organisms because anti-sense was a "highly unpredictable technology" and a "high quantity of experimentation" would be needed to practice the invention outside of the disclosed example); *Vaeck*, 947 F.2d at 495-96, 20 USPQ2d at 1444-45 (holding the examiner did not err in rejecting as nonenabled claims drawn to all genetically-engineered cyanobacteria expressing a given protein because the claimed 150 genera of cyanobacteria represent a vast, diverse, and poorly understood group; heterologous gene expression in cyanobacteria was "unpredictable"; and the patent's disclosure referred to only a genus). The district court found that a skilled artisan could readily have used various cultured vertebrate and mammalian cells to produce human EPO, and this fact was buttressed by numerous post-filing publications that demonstrated the extent of the enabling disclosure. *Amgen*, 126 F. Supp. 2d at 162, 57 USPQ2d at 1517 (citing *Gould v. Quigg*, 822 F.2d 1074, 3 USPQ 1302 (Fed. Cir. 1987) for the proposition that an expert may rely on post-filing publications to show enablement). The court also found that for those skilled in the art it was a relatively simple matter to determine whether a certain promoter would work within a specific vertebrate cell, whether a particular vertebrate cell would produce human EPO in culture, and whether a particular promoter could be operatively linked to control the transcription of the human EPO DNA. *Id.* In summary,

the court once again chose to credit Amgen's witnesses, Drs. Lodish and Wall, on the issue of enablement:

> Throughout the testimony of these witnesses, a theme becomes apparent: any challenge which one of ordinary skill in 1984 might have encountered in attempting to make and use the claimed invention using other cultured mammalian cells could be resolved by experimentation falling short of undue.

Id. at 159, 57 USPQ2d at 1515.

With these factual findings before us, TKT cannot prevail simply by reasserting in a conclusory manner that Amgen's disclosure does not enable the transformation of all mammalian or vertebrate cells or the production of human EPO. The district court carefully considered these issues, finding in the end that TKT had not met its clear and convincing burden of proof. Finding no clear error in these factual determinations, and having been directed to no legal error committed by the trial court, we will not disturb its holding that the asserted patents are not invalid for failure to meet the enablement requirement of § 112 ¶ 1.

C

Certain concerns are raised by the dissent. My brother in dissent sees the district court as having "abstained from fully inquiring" about compliance with the written description and enablement requirements of § 112, ¶ 1. In light of this strong statement, we write here to highlight what the district court did and did not do in deciding the case below. The district court should be seen as deciding the challenges to validity under each requirement as presented to it by the accused infringer. In doing so, the court fully found the facts that under-girded its conclusions on validity and relied on our case law interpreting and applying § 112. We are largely limited on review to deciding whether those findings based on that testimony are clearly erroneous and we cannot so

conclude. We may, of course, review *de novo* the court's interpretation of our precedent.

The dissent, however, does not directly challenge the court's factual findings, nor does it mention the decisions relied on by the district court. Instead, it finds fault in the absence of discussion of other precedents, namely *Eli Lilly, Gentry Gallery, In re Mayhew*, and *In re Vaeck*, and makes broader arguments seemingly based upon policy considerations.

The dissent would vacate and remand the written description issue because the district court did not cite our precedents *Eli Lilly* and *Gentry Gallery*. According to the dissent, the district court "did not focus on the correct law to be applied" and, for that reason, its "factual findings merit no deference." It is difficult to see how the district court's analysis must be rejected because it did not include discussions of these two decisions or, per the dissent, "the principles they espouse." First, it is far from clear that the defendant based its written description challenge below primarily on these two cases. Second, as we hold above, these cases are simply inapplicable here. Given these considerations, we decline to hold that the failure of the district court to cite these precedents constitutes reversible error.

In addressing the enablement inquiry the dissent looks to two other cases not discussed by the district court. It cites *In re Mayhew*, 527 F.2d 1229, 1233, 188 USPQ 356, 358 (C.C.P.A. 1976), for the proposition that "claims failing to recite a necessary element of the invention fail for lack of an enabling disclosure." There, however, the method claims omitted a step without which the invention as claimed was wholly inoperative (meaning it simply would not work and could not produce the claimed product). *Id.* Here, the lack of a limitation directed to the exogenous expression vector in the product claims is not a failure to describe the structure of the cell or a necessary element of the claimed EPO. Once inside

the cell, the transcription control sequence and the human EPO DNA integrate randomly into the host cell chromosomes. The only required description, then, is of the EPO DNA and the transcription control sequences because it is the presence of these sequences in the cell that causes the cell to produce the EPO as claimed. Thus, the lack of a description of (or a limitation directed to) the expression vector itself (as separate from the EPO DNA and transcription control sequences) does not render the invention inoperable and therefore does not run afoul of *In re Mayhew*, 527 F.2d at 1233, 188 USPQ at 358 (affirming examiner's rejection of claims not limited to having a cooling zone at the exit of a steel strip from a zinc bath because the specification indicated that without that cooling bath the invented process would not work).

The dissent's reliance on *In re Vaeck* is also misplaced. *Vaeck* is cited for the proposition that the disclosure of one or two species (here monkey and hamster cells) "may not enable a broad genus under the circumstances." 947 F.2d at 496, 20 USPQ2d at 1444-45. But then again, it may; the inquiry is fact-specific. Here the district court held the disclosure did enable the genus because the differences between using the two described mammalian (and vertebrate) cells and other such cells were small and easily accommodated by the artisan. Thus, in assessing the evidence, the court found that the defendant's evidence fell short of clear and convincing.

But more fundamentally, we think the dissent unfairly characterizes the district court's careful and reasoned handling of the § 112 issues. The dissent repeatedly suggests that the district court "simply refused" to consider whether, having disclosed only one means to make EPO produced by vertebrate or mammalian cells, Amgen was entitled to claims for all such cells and EPO. Specifically, the dissent asserts that the district court "abstained" from considering whether the absence of a claim limitation on the means of expression

raises § 112 issues.[11] We find this hard to understand. The district court explicitly analyzed these requirements in addressing defendant's specific challenges to validity. It decided they were not proven sufficiently and its decision is supported both by citations to our precedent and its own factual findings. Thus, rather than refusing to answer the § 112 questions, it seems the district court did answer them affirmatively.

In addressing this specific issue, the district court relied principally on two of our precedents: *Phillips Petroleum* and *Cellpro*. The court construed the former as not requiring the written description to include later-developed methods for making a claimed product. *Amgen*, 126 F. Supp. 2d at 150, 160, 57 USPQ2d at 1508, 1515. The court construed the latter as holding that a product claim is supported by adequate written description and enabling disclosure even if it describes only one method of making the claimed product. *Id.* at 160, 57 USPQ2d at 1515. These cases have not been shown to be incorrectly applied by the district court. And we, like the district court, are obligated to follow them both, as they explicitly support the court's rulings. *Phillips Petroleum*, 865 F.2d at 1251, 9 USPQ2d at 1465 (holding that the patentee was entitled to a prior filing date because the earlier disclosure of polypropylene as known at that time described and enabled a later claim to "[n]ormally solid polypropylene" even though a new, higher molecular weight form of polypropylene had been subsequently discovered), and *Cellpro*, 152 F.3d at 1361, 47 USPQ2d at 1719 (affirming summary judgment of enablement of a product claim over a challenge that two alternative embodiments disclosed in the patent were not enabled because "the enablement requirement is met if the description enables any mode of making and using the invention").

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[11] In this same vein, the dissent suggests that our court here has somehow "waived" the requirements of § 112 for product claims.

Rather than addressing these precedents, the dissent makes broad arguments that are not specifically grounded in our precedent. The dissent asks whether Amgen's disclosure "entitles it to claim *all* EPO produced by mammalian cells in culture, or *all* cultured vertebrate cells that produce EPO." (emphasis in original). While this broad entitlement question may be important as a policy matter, where, as here, we have applicable precedents, we are bound by the specific inquiries they mandate. Here, we, as did the district court, look to the requirements of § 112 as interpreted by our precedent. In short, the district court cannot have committed legal error by faithfully following controlling precedent of this court.

Lastly, the dissent emphasizes that omissions in the claim limitations and in the disclosures of the specifications "raised enablement issues." If the claims were still in prosecution before the PTO, perhaps the examiner could make an issue of such omissions. The dissent talks of what is "essential for the *patentability* of the claims." (emphasis added). But the question here is not patentability of application claims, but validity of issued claims that are presumed valid by statute. Now a heavy burden falls on the challenger. The district court found that the challenger had not carried that burden. It admitted that the questions were close—indeed, it found invalidity proven, but only by a preponderance. Hence, rather than refusing to decide questions of validity under § 112, it did decide them under the proper standard of proof. We see no reversible error.

III

Having addressed the claim interpretation and § 112 issues, we move to the second step of the infringement analysis: comparison of the properly construed claims to the accused product or process. *See, e.g., CCS Fitness*, 288 F.3d at 1365, 62 USPQ2d at 1662. Our review of this step differs depending upon whether the issue of infringement was resolved on summary judgment or after a full trial. *See Cole v. Kimberly-*

Clark Corp., 102 F.3d 524, 528, 41 USPQ2d 1001, 1004 (Fed. Cir. 1996). In the case of summary judgment, as with claim 1 of the '422 patent, we review *de novo* the trial court's finding that there was no genuine issue as to any material fact regarding infringement. *Id.*, 41 USPQ2d at 1004; Fed. R. Civ. P. 56(c). After a full bench trial, infringement is a question of fact that we review, of course, for clear error. *Ultra-Tex Surfaces, Inc. v. Hill Bros. Chem. Co.*, 204 F.3d 1360, 1363, 53 USPQ2d 1892, 1895 (Fed. Cir. 2000). When JMOL is entered under Fed. R. Civ. P. 52(c), as with the '698 and '080 patents, we review the district court's determination for clear error, as if it had been entered at the close of all the evidence. *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343, 56 USPQ2d 1641, 1643 (Fed. Cir. 2000). Anchored in the proper scope of review for each claim in dispute, we now address the trial court's infringement analysis.

A. The '933 Patent

Amgen asserted the following three claims of the '933 patent against TKT:

> 1. A non-naturally occurring erythropoietin glycoprotein product having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and having glycosylation which differs from that of human urinary erythropoietin.
>
> 2. The non-naturally occurring EPO glycoprotein product according to claim 1 wherein said product has a higher molecular weight than human urinary EPO as measured by SDS-PAGE.
>
> 9. A pharmaceutical composition comprising an effective amount of a glycoprotein product effective for erythropoietin therapy according to claim 1, 2, 3, 4, 5, or 6 and a pharmaceutically acceptable diluent, adjuvant or carrier.

Critical for our purposes is the final limitation of claim 1, which states that the claimed glycoprotein has "glycosylation which differs from that of human urinary erythropoietin." Glycosylation is the addition of carbohydrate side chains to amino acid residues in protein sequences to form glycoproteins. *Encyclopedia of Molecular Biology* at 1047. At the *Markman* hearing, Amgen asserted that the phrase meant "the attached carbohydrate groups differ when analyzed by standard prior art techniques known as of 1983-84." TKT argued, by contrast, that it meant "the carbohydrate groups attached to side chains of the erythropoietin polypeptide backbone differ by Western blot analysis and SDS/PAGE and carbohydrate composition analysis from those of human urinary erythropoietin to at least the degree described in the patents-in-suit."

Thus, the primary difference concerned which, if any, techniques were acceptable to determine whether the glycosylation was different. The district court found that the examples in the specification teach three measurement methods, but that they failed to limit "glycosylation which differs" to those methods. The court ruled, therefore, that the phrase means: "Glycosylation as to which there is a detectable difference based upon what was known in 1983-1984 from that of human urinary erythropoietin, having in mind that the patent holder, Amgen, taught the use of this Western blot, SDS-PAGE and monosaccharide test." *Amgen*, 126 F. Supp. 2d at 91-92, 57 USPQ2d at 1463.

It is undisputed that in 1983, there were at least two analytical techniques available for detecting differences in glycosylation between two glycoproteins. SDS-PAGE is a type of gel electrophoresis in which the glycoprotein of interest is bound to a charged compound that denatures the glycoprotein, which in turn is subjected to an electric field; glycoproteins of different molecular weight (reflecting their different glycosylations) will migrate through the electric

field at different speeds. *Id.* at 124, 57 USPQ2d at 1488. Isoelectric focusing ("IEF"), a second technique known to artisans in 1983, is similar to SDS-PAGE except that it determines the pH at which a protein is electrically neutral because the charge is placed in the gel in the form of a pH gradient, rather than on the glycoprotein itself. *Id.* at 125, 57 USPQ2d at 1488. The data obtained by both these methods can be visualized by Western blot, allowing an approximation of the molecular weight.

There was little dispute that any of these tests could be used to determine the glycosylation of a glycoprotein. Indeed, the district court noted that the testimony of an Amgen witness, Dr. Cummings, "would discharge Amgen's duty of showing by a preponderance of the evidence that HMR4396 has glycosylation which differs from that of human urinary EPO." *Id.* at 127, 57 USPQ2d at 1490. However, the court also credited evidence that indicated two uEPO preparations produced from the same batch of starting materials could nevertheless have different glycosylation patterns. *Id.* at 129, 57 USPQ2d at 1492 ("[A] skilled artisan in 1984 would have understood that urinary erythropoietin samples obtained using different purification methods could have different glycosylation. As a result, the glycosylation of human urinary erythropoietin was in 1984, and continues to be, a moving target."). Consequently, because the district court concluded that the patent failed to identify a single standard by which the "difference" could be measured, it held that TKT did not infringe and the '933 patent was invalid for failure to satisfy 35 U.S.C. § 112:

> The claim language of the '933 patent, however, presupposes that the glycosylation of urinary erythropoietin is a fixed, identifiable marker against which the glycosylation of recombinant EPOs can be measured. Yet, how can one prove that a recombinant EPO has glycosylation which differs from that of urinary EPO when the glyco-

> sylation of urinary EPO itself varies? The Court need not answer this conundrum. All that need be said is that Amgen's showing that GA-EPO has glycosylation which differs from but one of the many heterogeneous urinary EPOs is insufficient to carry its burden of proving infringement by a preponderance of the evidence that TKT infringes the claim limitation.

Id. at 129, 57 USPQ2d at 1492.

Amgen argues on appeal that an ordinarily skilled artisan in 1984 would have understood, based upon the patent disclosure, that there were two principal processes for purifying uEPO, with the technique taught by Miyake (SDS-PAGE) recognized as the standard. It asserts that it carried its burden of proving infringement because its empirical evidence "unequivocally demonstrated the glycosylation difference between Miyake-purified uEPO and the accused product." But it seems to us that Amgen has failed to address the trenchant question on this issue, *i.e.*, whether uEPO is necessarily glycosylated in the same way. Amgen deals rather cavalierly with the question in both its principal and reply brief, stating summarily that the district court erred and suggesting that the question is unimportant.

By definition, one must know what the glycosylation of uEPO is with certainty before one can determine whether the claimed glycoprotein has a glycosylation different from that of uEPO. In its discussion characterizing recombinant glycoprotein products, the specification of the '933 patent does not direct those of ordinary skill in the art to a standard by which the appropriate comparison can be made. *See* '933 patent, col. 28, line 33 - col. 29, line 7. The district court considered evidence that experiments conducted by Amgen in 1984 showed that different urinary EPO preparations had different glycosylation. For example, EPO purified from the urine of a single patient ("Lot 82") using a modified Miyake procedure was shown to have a different glycosylation from

other human uEPO (taken from Goldwasser). *Amgen*, 126 F. Supp. 2d at 129, 57 USPQ2d at 1491-92. And so, even assuming that Amgen is correct that one of ordinary skill in the art would have understood the benchmark test for glycosylation to be Miyake, its contention still fails. As the district court noted, the Miyake article provides a method of purification, but hardly suggests uniformity of glycosylation of the human uEPO studied:

> The 1977 Miyake et al. publication, for example, describes the purification from the same starting material of two homogeneous urinary EPO preparations (Fraction II and Fraction IIIA) that had about the same potency in terms of biological activity. Fractions II and IIIA . . . had different carbohydrate compositions and, therefore, differed from each other in glycosylation. Thus, these two uEPO preparations, though produced by the same procedure (*Miyake) and derived from the same batch of starting material, nonetheless had different glycosylation.

Id. at 129, 57 USPQ2d at 1491; *see also* Miyake, *Purification of Human Erythropoietin*, J. Bio. Chem. 5558, 5562 (1977) ("In spite of our finding of similar potency and molecular size, these two preparations [Fractions II and IIIA] must be considered different. The chemical basis for this difference is now being studied."). Amgen fails to controvert or otherwise address this evidence in its cross-appeal.

Under 35 U.S.C. § 112 ¶ 2, a patent applicant is required, at the close of his specification, to "particularly point[] out and distinctly claim[] the subject matter the applicant regards as his invention." The requirement of claim definiteness set out in § 112 ¶ 2 assures that claims in a patent are "sufficiently precise to permit a potential competitor to determine whether or not he is infringing." *Morton Int'l, Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470, 28 USPQ2d 1190, 1195 (Fed. Cir. 1993). The standard of indefiniteness is somewhat high; a claim is not indefinite merely because its scope

is not ascertainable from the face of the claims. *Cf., e.g., LNP Eng'g Plastics, Inc. v. Miller Waste Mills, Inc.*, 275 F.3d 1347, 1359-60, 61 USPQ2d 1193, 1202 (Fed. Cir. 2001) (affirming district court finding that patent was not indefinite, despite testimony from a co-inventor that he did not understand what the claim limitation "substantially completely wetted" meant). Rather, a claim is indefinite under § 112 ¶ 2 if it is "insolubly ambiguous, and no narrowing construction can properly be adopted." *Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371, 1375, 60 USPQ2d 1272, 1276 (Fed. Cir. 2001); *Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1349, 63 USPQ2d 1769, 1776 (Fed. Cir. 2002) ("It is not our function to rewrite [indefinite] claims to preserve their validity."). Applying these legal maxims to the facts of this case, we agree with the district court that the claims requiring "glycosylation which differs" are invalid for indefiniteness.

We find erroneous, however, its conclusion that invalidity for indefiniteness should be found only in the alternative. A claim is indefinite if, when read in light of the specification, it does not reasonably apprise those skilled in the art of the scope of the invention. *See Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1378, 55 UPQ2d 1279, 1282 (Fed. Cir. 2000) (citing *Personalized Media Comm., LLC v. ITC*, 161 F.3d 696, 705, 48 USPQ2d 1880, 1888 (Fed. Cir. 1998)). So it is here. Recognizing that it was faced with a "conundrum" regarding claim construction, the court held that the patent was not infringed because Amgen could not meet its burden simply by showing "that GA-EPO has glycosylation which differs from but one of the many heterogeneous urinary EPOs." *Amgen*, 126 F. Supp. 2d at 129, 57 USPQ2d at 1492. That the court recognized that one of ordinary skill in the art would have been faced with this "conundrum" should have ended the inquiry, for such ambiguity in claim scope is at the heart of the definiteness requirement of 35 U.S.C. § 112 ¶ 2. One cannot logically determine whether an accused product

comes within the bounds of a claim of unascertainable scope. Accordingly, the finding that TKT does not infringe the '933 patent is vacated and the finding that the '933 patent is invalid under § 112 is affirmed.

B. The '080 Patent

Claims 2-4 of the '080 patent are at issue:

> 2. An isolated erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6 and is not isolated from human urine.
>
> 3. A non-naturally occurring erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6.
>
> 4. A pharmaceutical composition comprising a therapeutically effective amount of an erythropoietin glycoprotein product according to claim 1, 2, or 3.

The critical limitation of the asserted claims in the '080 patent is the requirement that the erythropoietin glycoprotein "comprise[] the mature erythropoietin amino acid sequence of Fig. 6." The court construed the claim term "mature erythropoietin amino acid sequence of Figure 6" that appears in claims 4 and 6 of the '698 patent and claims 2 and 4 of the '080 patent. The dispute here arises out of a mistake in the specification. At the time the patent was drafted, it was believed that the sequence included 166 amino acids, and this belief is depicted in Figure 6. In fact, later research demonstrated that the full sequence was actually *165* amino acids; the last (arginine) is actually cleaved off prior to the

protein's secretion from the cell. Amgen argued that the reference to Figure 6 was irrelevant, even if the figure had too many amino acids, because it still showed the "mature [i.e., 165] erythropoietin amino acid sequence." TKT argued that the reference to Figure 6 required the term to be construed as depicted in Figure 6, and thus with 166 amino acids. Following trial,[12] the court adopted TKT's proposal, relying on what it considered key language in the specification supporting that construction: "Fig. 6 thus serves to identify the primary structural conformation (amino acid) sequence of mature human EPO as including 166 specified amino acid residues . . . ." '080 patent, col. 12, lines 3-5. *Amgen*, 126 F. Supp. 2d at 86-87, 57 USPQ2d at 1459.

In total, Figure 6 consists of five separate figures denominated Figs. 6A through 6E, which collectively disclose the sequence of human genomic EPO DNA and the encoded EPO. The detailed description in the '080 patent indicates that the specificity of Figure 6 is not to be lightly disregarded:

> Fig. 6 thus serves to identify the primary structural conformation (amino acid sequences) of mature human EPO as including 166 specified amino acid residues (estimate M.W.=18,399). Also revealed in the Figure is the DNA sequence coding for a 27 residue leader sequence along with 5' and 3' DNA sequences which may be significant to promoter/operator functions of the human gene operon. Sites for potential glycosylation of the mature human EPO polypeptide are designated in the Figure by asterisks. It is worthy of note that the specific amino acid sequence of Fig. 6 likely constitutes that of a naturally occurring allelic form of human erythropoietin. Support for this position is found in the results of

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[12] The court declined to rule on this issue at the *Markman* hearing, instead choosing to take the matter under advisement. See 126 F. Supp. 2d at 87, 57 USPQ2d at 1459.

> continued efforts at sequencing of urinary isolates of human erythropoietin which provided the finding that a significant number of erythropoietin molecules therein have a methionine at residue 126 as opposed to a serine as shown in the Figure.

'080 patent, col. 21, lines 29-40.

When the district court revisited the "Figure 6" issue, it concluded that the language of the claims, read in conjunction with the portion of the specification excerpted above, clearly identified the mature erythropoietin amino acid sequence as exactly depicted in Figure 6. In so doing, the court expressly rejected Amgen's contention that the claim should be read as covering the mature amino acid sequence, of erythropoietin, whatever its number of amino acids. *Amgen*, 126 F. Supp. 2d at 100, 57 USPQ2d at 1470 ("Had Amgen claimed only 'the mature erythropoietin amino acid sequence' without associating or linking that amino acid sequence to Figure 6 its argument that its claims cover whatever sequence (whether it contained 165 or 166 amino acids) is ultimately secreted by the cell might have more momentum."). The district court therefore found at the close of Amgen's case that HMR4396 does not literally infringe the asserted claims of the '080 patent.

The issue of infringement under the doctrine of equivalents was much closer, and likewise centered on the "Figure 6" limitation.[13] The district court concluded that Amgen had proven by a preponderance of the evidence that the 165 amino acid sequence satisfied the function-way-result test, crediting in particular the testimony of Dr. Lodish that TKT's

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[13] The district court held that every other limitation of the asserted claims in the '698 patent were met literally by the accused product/process. *Amgen*, 126 F. Supp. 2d at 132-33, 57 USPQ2d at 1493. Thus, whether equivalent infringement occurred turned on whether the "Figure 6" limitation was equivalently met.

missing arginine residue (the 166th amino acid appearing in Figure 6) does not affect the *in vivo* biological activity of its EPO product. *Id.* at 133, 57 USPQ2d at 1495. In reaching its conclusion, the court rejected TKT's argument that Amgen was not entitled to any range of equivalents under *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki*, 234 F.3d 558, 566, 56 USPQ2d 1865, 1870 (Fed. Cir. 2000), because during prosecution it had narrowed the scope of the claim for reasons related to patentability. The parties have cross-appealed on this patent, with Amgen asserting that the district court erred by finding no literal infringement and TKT continuing to press its estoppel theory as a basis for denying any range of equivalents.

Naturally, Amgen continues to focus on the "mature" portion of the relevant claim limitations to support its argument that the trial court erred by finding no literal infringement. According to Amgen, the practical result of the trial court's conclusion is to read out from the claims the preferred embodiment of the invention because the specification makes clear that "mature" human EPO is that form which circulates in the blood, *i.e.*, the 165 amino acid form that has already been secreted. This argument strains reason to its breaking point; our reading of the patent, like the district court's, will support no such interpretation.

Amgen's argument is based upon a misconstruction of the term "including" that evinces a misunderstanding of the plain meaning of that term, as well as the term "comprise," which appears in the '080 patent claims.[14] "Comprising is a term of

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[14] Amgen argues: "The specification describes the mature amino acid sequence of human EPO as 'including'—not 'limited to'—the 1-166 sequence. Properly construed, Lin's claimed sequence—the mature sequence—includes the fully processed form of any glycoprotein having the Figure 6 sequence. That includes both the 1-165 and the 1-166 amino acid sequences of Figure 6. Only this construction affords 'mature' its proper meaning, and includes Lin's preferred embodiment."

art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1633 (Fed. Cir. 1997). The word "include" means the same thing. *See Hewlett-Packard Co. v. Repeat-O-Type Stencil Mfg. Corp., Inc.*, 123 F.3d 1445, 1451, 43 USPQ2d 1650, 1655 (Fed. Cir. 1997) ("The claim term 'including' is synonymous with 'comprising,' thereby permitting the inclusion of unnamed components."); *see also Webster's II New Riverside University Dictionary* 619 (1984) ("*include*: 1. To have or take in as a part or member: CONTAIN; 2. To put into a group class, or total."). Thus, a claim reciting "a widget comprising A and B," for example, would be infringed by any widget containing A and B, no matter that C, D, or E might be present.

If, then, as the specification states, "the primary structural conformation (amino acid sequence) of mature human EPO as including 166 specified amino acid residues," it is simply illogical for Amgen to argue that that means anything other than, at minimum, the 166 amino acids shown in Figure 6. This is verified by the fact that '080 claims 2 and 3 claim an erythropoietin glycoprotein "*compris[ing]* the mature erythropoietin amino acid sequence of Fig. 6 . . . ." Again, read properly in light of the term "comprising," this means that the claimed glycoprotein must have—at minimum—all 166 amino acids shown in Figure 6.

Turning to the finding of infringement under the doctrine of equivalents, TKT asserts that Amgen should be estopped from obtaining such coverage under *Festo*. Specifically, TKT alleges that the "mature amino acid sequence of Figure 6" limitation that appears in the '080 patent was added to overcome a double-patenting rejection, and therefore constitutes an amendment related to patentability. We agree.

The district court correctly found that the amendment, although voluntary, was made to avoid a "same invention" double patenting rejection, *Amgen*, 126 F. Supp. 2d at 135, 57 USPQ2d at 1496, and although the Supreme Court reversed our decision in *Festo* and rejected the notion of an absolute bar to the doctrine of equivalents, it agreed with our holding "that a narrowing amendment to satisfy any requirement of the Patent Act may give rise to an estoppel." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki*, 535 U.S. 722, 122 S. Ct. 1831, 1839 (2002). Contrary to the district court's conclusion, "'[s]ame invention' double patenting is based upon 35 U.S.C. § 101, which states that an inventor may obtain 'a patent' for an invention." *In re Lonardo*, 119 F.3d 960, 965, 43 USPQ2d 1262, 1266 (Fed. Cir. 1997) (emphasis added). Therefore, the district court's finding of equivalent infringement of the '080 patent is vacated and remanded for an analysis under the narrow ways of rebutting the Supreme Court's presumption of estoppel. *Festo*, 122 S. Ct. at 1839.

C. The '698 Patent

The '698 patent is directed generally to a process for producing a glycosylated erythropoietin polypeptide. Claims 4-9 are at issue. Independent claims 4 and 6 read as follows:

> 4. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps:
>
> a) growing, under suitable nutrient conditions, vertebrate cells comprising promoter DNA, other than human erythropoietin promoter DNA, operatively linked to DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and
>
> b) isolating said glycosylated erythropoietin polypeptide expressed by said cells

> 6. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:
>
> a) growing, under suitable nutrient conditions, vertebrate cells comprising amplified DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and
>
> b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.

Infringement of dependent claims 5 and 7-9 rises or falls with the analysis that applies to independent claims 4 and 6.[15] The phrase "operatively linked" appears in claim 4 of the '698 patent, and is related by dependency to claims 5 and 9. According to the district court, the phrase relates to the relationship between promoter DNA and the DNA that is transcribed downstream from the promoter DNA. Amgen contended that the phrase means "positioned such that it provides for initiation of transcription of a gene." TKT argued that the term means positioned adjacent "to the DNA encoding EPO in a way that maintains the capability to initiate transcription of EPO DNA." In other words, Amgen argued that the words "operatively linked" imposed no spatial restriction, whereas TKT contended that because the patent allegedly taught placing the promoter DNA immediately adjacent to the DNA encoding EPO, the term "operatively linked" ought be limited

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[15] Claim 5 claims "[t]he process of claim 4 wherein said promoter DNA is viral promoter DNA." Claim 7 claims "[th]e process of claim 6 wherein said vertebrate cells further comprise amplified marker gene DNA." Claim 8 claims "[t]he process of claim 7 wherein said amplified marker gene DNA is Dihydrofolate reductase (DHFR) gene DNA." And claim 9 claims "[t]he process according to claims 2, 4 and 6 wherein said cells are mammalian cells."

by location. The district court held that the term "operatively linked" means "the promoter DNA is linked to the EPO DNA is such a way that maintains the capability of the promoter DNA to initiate transcription of the EPO DNA." *Amgen*, 126 F. Supp. 2d at 90, 57 USPQ2d at 1462.

The district court granted TKT summary judgment of non-infringement of independent claims 4 and 6 (and hence dependent claims 5 and 7-9) of the '698 patent because it found that Amgen had failed to carry its Rule 52(c) burden. *Id.* at 102, 57 USPQ2d at 1471. Amgen assails this conclusion as not in accordance with law, inasmuch as the differences considered dispositive by the district court are not claimed and thus have no bearing on a proper infringement analysis. In fact, according to Amgen, the district court neglected to identify any limitation of the '698 patent that the accused process fails to literally meet, and also failed to explain why, in the absence of literal infringement, those limitations were not otherwise equivalently met. We agree with Amgen, and therefore conclude *vacatur* is appropriate.

The district court properly recognized that the infringement analysis of process claims is necessarily different from that for product claims. *See id.* at 102, 57 USPQ2d at 1471 ("The process patent gives notice to competitors that the steps described therein are not to be repeated to achieve the same result. Thus, whereas in the product patent context, differences in process are meaningless, here, in the process patent context, these differences mean everything."). But after a correct discussion of the differences in the infringement analysis, the court eschewed the cardinal principle that the accused device must be compared to the claims rather than to a preferred or commercial embodiment. *Id.* ("Based on . . . *the many differences between Amgen's and TKT's processes* . . . Amgen's proof of infringement on the '698 patent [is] insufficient . . . .") (emphasis added).

For example, the court concluded that a fundamental distinction between the respective processes was that TKT employs homologous rather than heterologous recombination, whereas "[i]n order to make EPOGEN®, Amgen transfects [CHO] cells with a vector that contains both viral promoter DNA and the human EPO gene." *Id.* This clear reference to the preferred embodiment of Example 10, which the district court considered "the process most heavily relied upon by Amgen in its patent," *id.* at 103, 57 USPQ2d at 1472, misses the point that none of the claims at issue contain such a limitation. And apart from the limitations of the asserted claims, the differences in the two processes are wholly irrelevant to the infringement analysis.

The district court likewise found material the fact that TKT places its promoter and enhancer farther upstream than does Amgen. In light of the court's claim construction, however, it would seem TKT satisfies the "operatively linked" limitation, as there is no question that TKT's promoter causes its intended functional effect. In any event, the trial court once again compared the accused process by reference to an example rather than the *claimed* process:

> As explained in Example 7 and illustrated in Figure 4, Amgen created the vector by cleaving, with BstEII restriction endonucelases . . . 'at a position which is 44 base pairs 5' to the initiating ATG coding for the pre-peptide and approximately 680 base pairs 3' to the HindIII restriction site' . . . . TKT's process has within the DNA sequence upstream of the codons that express the EPO polypeptide several ATG sites . . . . The court finds that such a process is sufficiently different from that encompassed by Amgen's invention that judgment of non-infringement should follow.

Id.

Again, this was legal error insofar as the infringement analysis is not tied to the asserted claims. We therefore vacate and remand so that the court may conduct a proper infringement inquiry in the first instance, comparing the accused device to the properly construed claims without limiting their scope to the examples in the specification or other limitations that are not properly a part of claims 4-9.

D. The '422 Patent

Claim 1 of the '422 patent, the only one in dispute, claims "[a] pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture." In the *Markman* hearing, Amgen contended the phrase "purified from mammalian cells grown in culture" meant "purified from the in vitro culture in which the mammalian cells have been grown," whereas TKT argued that it meant "obtained in a substantially homogeneous state from the mammalian cells in which it was produced and not from the cell culture media." Concluding that TKT's construction would exclude the patent's preferred embodiment (Example 10), the court read the phrase "mammalian cells grown in culture" as a whole to encompass purification techniques from the cells or the cell culture medium. *Id.* at 88-89, 57 USPQ2d at 1460-61. As indicated earlier, the district court immediately turned to and granted Amgen's motion for summary judgment of infringement of the '422 patent at the close of the *Markman* hearing.

According to the district court, it was clear from the beginning that the accused product met most limitations of claim 1. That HMR4396 was a pharmaceutical composition that contained a therapeutically effective amount of human erythropoietin was plain, in view of the Investigational New Drug Application ("INDA") that TKT filed with the Food and Drug Administration. *Id.* at 94-95, 57 USPQ2d at 1465. The

district court further concluded that HRM4396 contained "a pharmaceutically acceptable diluent, adjuvant or carrier" in view of the testimony of TKT's Rule 30(b)(6) designee, who testified that the HRM4396 recovered in bulk from the culturing of human cells was diluted with a phosphate buffer to control the pH and provide a product of desired strength. *See id.* at 95, 57 USPQ2d at 1466. The sole remaining issue, then, was whether the accused product was "purified from mammalian cells grown in culture." Rather than taking the utterly untenable position that humans are not mammals, TKT conceded infringement under the court's claim construction. *Id.* at 95, 57 USPQ2d at 1466.

TKT tries three different tactics on appeal to escape this concession of infringement. First, TKT argues that "mammalian cells," as the phrase is used in the '422 patent, do not include its cells because Amgen excluded the use of human cells to produce human EPO from its invention. Second, TKT asserts that the finding of infringement was in error because the patent specification defines pharmaceutical compositions "as comprising 'polypeptides of the invention'," and HRM4396 is not a "polypeptide of the invention" inasmuch as the invention is "uniquely characterized" by (and hence limited to) exogenous EPO DNA. Finally, TKT challenges the finding of infringement because, it asserts, the intrinsic evidence limits the phrase "purified from mammalian cells grown in culture" to purification that takes place inside the cells, and not—like TKT—from the culture media.[16] As infringement of the '422 patent was granted on summary judgment, we review the district court's conclusion *de novo*, applying the same standard applied by the trial court. *Schering Corp. v. Amgen, Inc.*, 222 F.3d 1347, 1351, 55

[16] The basis for this argument is that claim 2 of the '698 patent recites recombinant EPO "isolated from the host cell or the medium of its growth." Therefore, asserts TKT, "Amgen also knew how to claim what it now seeks, but failed to do so."

USPQ2d 1650, 1653 (Fed. Cir. 2000). Under this standard, we agree with the trial court that a grant of summary judgment of infringement of the '422 patent was warranted.

We cannot accept, for the reasons already stated, TKT's proposed reading of the claim term "mammalian" and its attempt to import the term exogenous into the claims; we therefore reject out of hand the contention that Amgen expressly excluded the use of human cells to express EPO and the use of endogenous DNA from the scope of its invention. Thus, the issue resolves to a narrow one: the accused product, HRM4396, infringes '422 patent claim 1 unless TKT is correct that the claim limitation "purified from mammalian cells grown in culture" means that the EPO product must be recovered directly from the cell, and not from the culture medium.

At the *Markman* hearing, Amgen contended the phrase means "purified from the in vitro culture in which the mammalian cells have been grown"; TKT argued that it means "obtained in a substantially homogeneous state from the mammalian cells in which it was produced and not from the cell culture media. The trial court read the phrase to encompass purification techniques from the cells or the cell culture medium because to do otherwise, it found, would exclude the patent's preferred embodiment as disclosed in Example 10. *Amgen*, 126 F. Supp. 2d at 88-89, 57 USPQ2d at 1461.

Example 10 "describes expression systems employing Chinese hamster ovary (CHO) DHFR$^-$ cells and the selectable marker, DHFR." '422 patent, col. 25, lines 38-40. As a part of the description, the example discloses that gene amplification in cell culture media is possible to increase productivity of the targeted recombinant EPO product. After describing an example of such a gene amplification system, the specification goes on to state: "The productivity of the EPO producing CHO cell lines described above can be improved by appropriate cell culture techniques. The propagation of

mammalian cells in culture generally requires the presence of serum in the growth media. *A method for production of erythropoietin from CHO cells in media that does not contain serum greatly facilitates the purification of erythropoietin from the culture media." Id.*, col. 27, lines 8-14 (emphasis added). We agree with the district court that this disclosure—the undisputed preferred embodiment of the invention—contemplates purification of erythropoietin from the culture media. *See also* '933 patent, col. 28, lines 28-32 ("Mammalian cell expression products may be readily recovered *in substantially purified form from culture media* using HPLC (C4) employing an ethanol gradient, preferably at pH7." (emphasis added)).

TKT does not challenge the district court's conclusion regarding the disclosure of Example 10. Accordingly, TKT's challenge ultimately must fail unless we read the preferred embodiment out of the claims, but rare is the case where we should or will do so. A claim interpretation that reads out a preferred embodiment "is rarely, if ever, correct and would require highly persuasive evidentiary support." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583, 39 USPQ2d 1573, 1578 (Fed. Cir. 1996). We have done so only one time—in an instance where the patent applicant limited the full scope of the claim language to omit the preferred (and only disclosed) embodiment in order to overcome an examiner's rejection. *See Elektra Instr. S.A. v. O.U.R. Scientific Int'l, Inc.*, 214 F.3d 1302, 1308, 54 USPQ2d 1910, 1914 (Fed. Cir. 2000). The present case lacks the "persuasive evidentiary support" necessary for us to read the claims so as to exclude the preferred embodiment disclosed in Example 10; we therefore decline to do so.

E. The '349 Patent

The '349 patent contains one method claim and six product claims that are drawn generally to types of vertebrate cells grown in culture. At issue are claims 1, 3-4, and 6-7:

> 1. Vertebrate cells which can be propagated in vitro and which are capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay, said cells comprising non-human DNA sequences that control transcription of DNA encoding human erythropoietin.
>
> 3. Vertebrate cells according to claim 1 capable of producing in excess of 1000 U erythropoietin per 10^6 cells in 48 hours.
>
> 4. Vertebrate cells which can be propagated in vitro which comprise transcription control DNA sequences, other than human erythropoietin transcription control sequences, for production of human erythropoietin, and which upon growth in culture are capable of producing in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay.
>
> 6. Vertebrate cells according to claim 4 capable of producing in excess of 1000 U erythropoietin per 10^6 cells in 48 hours.
>
> 7. A process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, vertebrate cells according to claim 1, 2, 3, 4, 5, or 6.

Each of the claims contain the limitation "non-human DNA sequences that control transcription" that appears in claim 1 of the '349 patent or the limitation "transcriptional control DNA sequences, other than human erythropoietin transcription control sequences" that appears in claim 4 of the '349

patent. Transcription is the process whereby RNA polymerase copies genetic information contained in a DNA nucleotide sequence into an RNA sequence. It is a critical step in the expression of proteins like erythropoietin and is itself controlled by specific DNA sequences. According to the patent, "transcription control sequences" is the collective term for DNA sequences that not only "provide a site for initiation of transcription into mRNA," but also are capable of binding proteins that determine "the frequency (or rate) of transcriptional initiation." '349 patent, col. 2, lines 3-12.

Amgen contended that this phrase means "non-human DNA sequences that are able to initiate or regulate RNA synthesis from EPO DNA." TKT argued that the phrase means "DNA sequences which did not originate in the human genome, which initiate and regulate RNA synthesis of adjacent DNA, and which replace the human EPO transcription control sequences." By including the term "adjacent DNA" in its construction, TKT sought to require the DNA sequences that control transcription to be located in a position adjacent to the gene segment intended to be expressed. Furthermore, TKT contended that in order to "control" transcription, the DNA sequences must both initiate and regulate the transcription of a gene. Amgen objected to the use of "and," preferring a construction that required DNA sequences either to initiate or regulate transcription. Finally, the parties disagreed as to the meaning of "non-human." Amgen argued that "non-human" means "not part of the human genome," whereas TKT contended it meant "not originating in the human genome."[17]

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[17] The importance of this distinction is that, because it is scientifically arguable that viral DNA originates in the human genome, the viral promoter DNA that TKT employs thus might not fall within the meaning of the claim.

First, the court rejected TKT's position and concluded that "non-human" DNA sequences are DNA sequences that are "not part of the human genome." The court similarly rejected TKT's "adjacent" language because "no claim term could reasonably be construed to be limiting the transcription control DNA sequences by their location." Finally, the court held that DNA sequences that control transcription are DNA sequences that initiate and regulate the processes of transcription. *Amgen*, 126 F. Supp. 2d at 88, 57 USPQ2d at 1459-60.

The district court entered judgment of noninfringement for TKT on method claim 7 of the '349 patent under an identical rationale to that used to grant judgment of noninfringement for the method claims of the '698 patent. *Id.* at 122, 57 USPQ2d at 1486. As we have found the court's analysis with respect to the '698 patent to be legally unsupportable, *see supra* at 41-42, we likewise vacate the district court's judgment with respect to claim 7 of the '349 patent and remand for further consideration. As to the product claims of the '349 patent, the court held that each of claims 1, 3, 4, and 6 were literally infringed, and further held (alternatively) that claims 3 and 6 were equivalently infringed.[18]

Aside from the challenge, already rejected, to the trial court's construction of the term "vertebrate cells," TKT

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[18] We note also that the trial court granted summary judgment of infringement of the product claims of the '349 patent. It modified its summary judgment finding (but reached the same result) with respect to the "controlling transcription" limitation in light of extensive trial testimony. *Amgen*, 126 F. Supp. 2d at 118, 57 USPQ2d at 1485. Accordingly, unlike the other limitations in the '349 patent, we review the court's conclusion with respect to "controlling transcription" for clear error, even though it comes to us from a grant of summary judgment of infringement. Because TKT has not demonstrated clear error in the trial court's conclusion, we affirm the finding of infringement.

mounts a weak challenge to these findings of infringement apparently under the reverse doctrine of equivalents.[19]

Under the reverse doctrine of equivalents, an accused product or process that falls within the literal words of a claim nevertheless may not infringe if the product or process "is so far changed in principle from a patented article that it performs the same or a similar function in a substantially different way." *Graver Tank & Mfg. Co. v. Linde Air Prod. Co.*, 339 U.S. 605, 608-09, 85 USPQ 328, 330 (1950); *see generally* Donald S. Chisum, 5A CHISUM ON PATENTS §-18.04 (1999). This doctrine is equitably applied based upon underlying questions of fact, *see Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1581, 18 USPQ2d 1001, 1013 (Fed. Cir. 1991), when the accused infringer proves that, despite the asserted claims literally reading on the accused device, "it has been so changed that it is no longer the same invention." *Del Mar Avionics, Inc. v. Quinton Instr. Co.*, 836 F.2d 1320, 1325, 5 USPQ2d 1255, 1259 (Fed. Cir. 1987) (citing *Graver Tank*, 339 U.S. at 608-09).

We are not persuaded by TKT that this is a case where equity commands a determination of non-infringement despite its product literally falling within the scope of the asserted claims. TKT relies on findings of the district court regarding differences in the way the accused device controls transcription in the '698 patent. It is true, as Amgen candidly admits, that the method by which TKT controls transcription is not identical. Whereas the patent describes placing the

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[19] The sum total of TKT's challenge to the infringement finding, aside from the "vertebrate" issue, is as follows: "[TKT] also do[es] not use the 'transcription control sequences' of the '349 patent. As the court found, [TKT]'s transcription control sequences are not only structurally different from Amgen's sequences but also function in a different way. Because of those differences in structure and function, [TKT] do[es] not infringe the 'transcription control sequences' limitation in the '349 claims."

promoter DNA in close proximity, or even adjacent, to the EPO leader peptide, TKT places its promoter further upstream. But again, it is error to conduct infringement analyses in a vacuum, without reference to the claims at issue.

The vertebrate cells of the '349 patent, as claimed, are comprised of non-human DNA sequences that control transcription of DNA encoding human erythropoietin. And "control[ling] transcription of DNA encoding human erythropoietin" simply means initiating and regulating the process of transcription. *Amgen*, 126 F. Supp. 2d at 88, 57 USPQ2d at 1460. This limitation is met literally because the cytomegalovirus in TKT's R223 cells performs this function, *id.* at 118, 57 USPQ2d at 1484, notwithstanding TKT's reliance on the court's erroneous analysis of the '698 patent method claims.

IV

Our affirmance of the district court's findings that certain of the asserted claims are infringed is not yet the coup de grâce for TKT; non-frivolous validity issues remain. One of the statutory requirements for patentability is that the invention for which a patent is sought was not known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention by the applicant. *See* 35 U.S.C. § 102(a). Similarly, one is not entitled to a patent if the subject matter of the invention as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the invention is directed. *See id.* § 103. TKT relies particularly on two items of prior art that allegedly render certain of the asserted claims anticipated under § 102(a) or obvious under § 103. We discuss each in turn.

A

TKT contends the asserted claims are anticipated by the work of Dr. Eugene Goldwasser ("Goldwasser"). Beginning

in 1979-80, Goldwasser conducted a clinical study at the University of Chicago at Illinois in which he obtained a preparation of highly purified erythropoietin derived from human urine and administered approximately 10,000 units of human urinary EPO to three anemic patients. *Amgen*, 126 F. Supp. 2d at 111, 57 USPQ2d at 1478. Although this study showed an increase in reticulocyte count in all three patients, and an increase in erythroid cells, plasma iron clearance rate, and red cell mass in at least one patient, Goldwasser admitted that "[t]here was no significant change in hematocrit in any patient." *Id.* at 111-12, 57 USPQ2d at 1478. And because there was no increase in hematocrit, Goldwasser testified in his deposition that he considered the study a failure. The district court concluded, as a result, that the study could not be invalidating anticipatory prior art: "[A]nother's experiment, imperfect and never perfected will not serve either as an anticipation or as part of the prior art, for it has not served to enrich it." *Id.* at 112, 57 USPQ2d at 1479 (quoting *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1558, 225 USPQ 26, 33 (Fed. Cir. 1985)).

The district court similarly concluded that Goldwasser did not render the patents obvious. Of paramount importance to the court was the fact that the prior art references, including Goldwasser, lacked Amgen's disclosure of the genetic sequence of EPO and failed to describe any transcription control sequences. *Id.* at 115, 57 USPQ2d at 1481. The court also considered the secondary factors—particularly long-felt need and commercial success—to be of high importance. *Id.* at 116, 57 USPQ2d at 1482 ("Before the advent of Amgen's product, whether EPO could actually produce a sustainable increase in a patient's hematocrit was not known. Furthermore, Amgen's EPO product, which was the first EPO-containing pharmaceutical composition to obtain FDA approval, has greatly improved the quality of life of chronic renal failure patients throughout the world. As a result, Dr. Lin received widespread public acclaim for his work.").

TKT assigns error to the district court's alleged blind acceptance of Goldwasser's assertion that the test was a failure without considering the contemporaneous testimony of Goldwasser's collaborator, Dr. Baron, who reported to the Food and Drug Administration in 1984 that evidence of erythroid marrow stimulation was detected. In particular, according to TKT, the court erred by failing to "look[] at the definition of therapeutic effect in the specification." We agree that "therapeutically effective" must be defined in accordance with *Markman v. Westview Instruments* before this issue can be properly resolved, and we therefore vacate and remand for further proceedings with respect to Goldwasser.

For the *Markman* hearing in this case, ten terms were "pre-selected" based upon their relationship to Amgen's then-pending motion for summary judgment of infringement. *Id.* at 81, 57 USPQ2d at 1455. Whether those "pre-selected" terms were chosen by the court or the parties is unclear from the record, but what is clear is that "therapeutically effective" was not among them. And so the district court, assumedly viewing "therapeutically effective" as not in dispute, construed it in its discussion of the Goldwasser reference:

> Such evidence [of, e.g., increased erythroid marrow stimulation] should be outweighed by the fact that the *actual* production of mature red blood cells was not achieved and, as a result, hematocrit levels were unchanged. *Because an increase in hematocrit and hemoglobin levels is the true mark of therapeutic effectiveness*, Dr. Goldwasser's study, which revealed only inchoate indicators of red blood cell production, falls far short of anticipating claims requiring a therapeutic amount of human EPO.

Id. at 112, 57 USPQ2d at 1479 (second emphasis ours). Had "therapeutically effective" not been in dispute, no error would arise. A district court may—indeed, often must—interpret or define a term in the claims that is not in dispute in order to

provide a proper context for the discussion of the terms that are in dispute. *See, e.g., DeMarini Sports v. Worth, Inc.*, 239 F.3d 1314, 1323, 57 USPQ2d 1889, 1893-94 (Fed. Cir. 2001). But here, the term "therapeutically effective" is in dispute because it is central to whether Goldwasser is properly considered prior art. *See In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985) (holding that a non-enabled disclosure will not suffice as § 102 prior art).

Although the endgame in the treatment of chronically anemic patients is to increase the hematocrit, as recognized by the district court, the claim term "therapeutically effective" must be understood in light of the specification of which it is a part. And that specification appears to teach that results in addition to simply an increase in hematocrit can provide effective therapy. *See* '933 patent, col. 33, lines 19-31 ("[The claimed polypeptide products] are conspicuously suitable for use in erythropoietin therapy procedures . . . to develop any or all of the effects heretofore attributed in vivo to EPO, *e.g., stimulation of reticulocyte response . . ., erythrocyte mass changes . . ., and, as indicated in Example 10, increasing hematocrit levels in mammals*." (emphasis added)).

Amgen asserts that the district court's construction of "therapeutically effective" is supported by admissions of TKT's experts that the term means "increasing and maintaining the patient's hematocrit to normal or near normal levels." But the relevant question is not whether one of ordinary skill would so understand the term, but whether that term should be limited based upon the express disclosure in the specification. *CCS Fitness*, 288 F.3d at 1367, 62 USPQ2d at 1662-63 ("[A] claim term will not carry its ordinary meaning if the intrinsic evidence shows that the patentee distinguished that term from prior art on the basis of a particular embodiment, expressly disclaimed subject matter, or described a particular embodiment as important to the

invention."). If the claim term "therapeutically effective" encompasses the patient responses described in the specification, as it appears to us it does, then the Goldwasser study may constitute invalidating prior art under § 102(a) or § 103 even if he did not achieve his intended result. We therefore vacate the trial court's determination that Goldwasser cannot constitute prior art because the study was a failure. Resolution of the issue turns on the construction of the meaning of "therapeutically effective," which the trial court should have an opportunity to construe in the first instance under *Markman* principles. *See Bayer AG v. Biovail Corp.*, 279 F.3d 1340, 1349, 61 USPQ2d 1675, 1682 (Fed. Cir. 2002). Accordingly, on remand, the court should construe this term and, in light of that construction, should determine whether Goldwasser invalidates any of the asserted patents under 35 U.S.C. §§ 102(a) or 103.[20]

B

A second item of prior art germane to this appeal is United States Patent No. 4,377,513 ("Sugimoto"), issued in March 1983. Sugimoto discloses a process for producing human erythropoietin "characterized by multiplying human lymphoblastoid cells capable of producing human erythropoietin by transplanting said cells into a non-human warm-blooded animal body, or alternatively multiplying said cells by allowing said cells to multiply with a device by which the nutrient body fluid of a non-human warm-blooded animal is supplied to said cells, and allowing the cells multiplied by either of the above multiplication procedures to release

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[20] We note also that on remand when considering obviousness and anticipation issues relating to the '080 and '422 patents the district court should be cognizant of the rule that a claimed product shown to be present in the prior art cannot be rendered patentable solely by the addition of source or process limitations. *General Electric Co. v. Wabash Co.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293, 311 (1884).

human erythropoietin." Sugimoto, col. 1, lines 30-38. Given the similarity of Sugimoto's disclosure to the patents asserted by Amgen, TKT naturally raised Sugimoto as potentially invalidating prior art, even though Sugimoto had been before the examiner.

The district court concluded that Sugimoto was not prior art under 35 U.S.C. § 102(a) because it was not proven to be enabled. *Amgen*, 126 F. Supp. 2d at 108, 57 USPQ2d at 1476 ("In light of the intense competition that grew out of the race to make human EPO suitable for treatment of chronic anemia, one would imagine that if Sugimoto's invention were truly enabling, then he would have won that lucrative race."). On appeal, TKT argues that the trial court erred in placing on it the burden of proving enablement of Sugimoto, because United States patents—even those only asserted as prior art in an invalidity defense—are presumed enabled under 35 U.S.C. § 282. We agree that prior art patents are presumed enabled, but under authority going beyond § 282.

A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled. Long ago our predecessor court recognized that a non-enabled disclosure cannot be anticipatory (because it is not truly prior art) if that disclosure fails to "enable one of skill in the art to reduce the disclosed invention to practice." *In re Borst*, 345 F.2d 851, 855, 145 USPQ 554, 557 (C.C.P.A. 1962); *accord In re Donohue*, 766 F.2d at 533, 226 USPQ at 621. Thus, the critical issue here is not whether Sugimoto must be enabled, but rather whether it is the plaintiff or the defendant who bears the burden of proof with respect to that question.

On appeal, Amgen argues that there should be no presumption of enablement in this case because under § 282 courts only presume the claimed subject matter in a patent is enabled. Thus, Amgen argues, because only the unclaimed disclosures of Sugimoto are at issue here, no presumption of

enablement should apply. This argument is not relevant, however, because, as reasoned below, we do not only rely on § 282 as the source for a presumption. Instead, relying on our precedent, we hold a presumption arises that both the claimed and unclaimed disclosures in a prior art patent are enabled.

In patent prosecution the examiner is entitled to reject application claims as anticipated by a prior art patent without conducting an inquiry into whether or not that patent is enabled or whether or not it is the claimed material (as opposed to the unclaimed disclosures) in that patent that are at issue.[21] *In re Sasse*, 629 F.2d 675, 681, 207 USPQ 107, 111 (C.C.P.A. 1980) ("[W]hen the PTO cited a disclosure which expressly anticipated the present invention . . . the burden was shifted to the applicant. He had to rebut the presumption of the operability of [the prior art patent] by a preponderance of the evidence." (citation omitted)). The applicant, however, can then overcome that rejection by proving that the relevant disclosures of the prior art patent are not enabled. *Id.* We hold that an accused infringer should be similarly entitled to have the district court presume the enablement of unclaimed (and claimed) material in a prior art patent defendant asserts against a plaintiff. Thus, a court cannot ignore an asserted prior art patent in evaluating a defense of invalidity for anticipation, just because the accused infringer has not proven it enabled. Like the applicant in *ex parte* prosecution, however, the patentee may argue that the relevant claimed or unclaimed disclosures of a prior art patent are not enabled and

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[21] Additionally, we think it unwise as a matter of policy to force district courts to conduct a mini-trial on the proper claim construction of a prior art patent every time an allegedly anticipating patent is challenged for lack of enablement. As we frequently revisit district courts' determinations in matters of claim construction and validity, we are certainly aware that such a task can occupy a great deal of a court's resources. In any event, because the presumption outlined here does not rely on § 282, we see no reason to impose these burdens on litigants and the district courts.

therefore are not pertinent prior art. If a patentee presents evidence of nonenablement that a trial court finds persuasive, the trial court must then exclude that particular prior art patent in any anticipation inquiry, for then the presumption has been overcome.[22] Therefore, it was Amgen who bore the burden of proving the nonenablement of Sugimoto before the district court. TKT did not bear a bear burden of proving enablement.

Turning now to the district court's opinion, we think a fair reading is that the court, at least implicitly, put a burden of proving enablement of Sugimoto on TKT. The court began its analysis of Sugimoto by discussing evidence from Amgen and concluding "one would imagine that if Sugimoto's invention were truly enabling, then he would have won that lucrative race [to make human EPO suitable for treating anemia]." *Amgen*, 126 F. Supp. 2d at 108, 57 USPQ2d at 1476. Proceeding from that standpoint, the court analyzed whether TKT's evidence was sufficient "to counter" this apparent conclusion that Sugimoto was not enabled. *Id.* at 108-09, 57 USPQ2d at 1476. Next, the court concluded its discussion of the enablement of Sugimoto by stating "TKT provided no evidence adequate to overcome the presumption that the Patent Office correctly rejected the contention that Sugimoto was an anticipating reference." *Id.* at 109, 57 USPQ2d at 1477. Importantly, only after apparently concluding that Sugimoto was not enabled did the district court discuss whether Sugimoto contained each and every limitation of any of Amgen's claims. The logical implication being that the court concluded that because TKT had not proven the enablement of Sugimoto, it could not anticipate any of Amgen's claims. In sum, we determine that ultimately,

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[22] We note that by logical extension, our reasoning here might also apply to prior art printed publications as well, but as Sugimoto is a patent we need not and do not so decide today.

the district court placed the burden of proving the enablement of Sugimoto on TKT.

In addition, looking at the evidence Amgen did present, we cannot conclude the district court properly found Amgen had met any burden that the court did place on it. At trial Amgen's expert, Dr. Erslev, testified that "no one reported using Sugimoto's process to make a pharmaceutical composition of human EPO, nor has any patient ever been treated by any EPO produced by the Sugimoto procedure." *Id.* at 108, 57 USPQ2d at 1476. The mere fact that no one *has* so used the Sugimoto process is only minimally probative of nonenablement: a conclusion that no one *could have* used Sugimoto. Amgen also pointed out that Sugimoto was before the patent examiner during the prosecution of Amgen's patents. *Id.* While this was true, Sugimoto's non-enablement was only one of several arguments Amgen presented to overcome a rejection during prosecution and the examiner did not state his agreement with this position when he allowed the patent. Because we cannot assume the acceptance of every argument presented during prosecution, the mere fact this argument was made is also only minimally probative of the enablement of Sugimoto. In sum, the evidence presented by Amgen was insufficient to meet the burden Amgen apparently was assigned.

We must therefore conclude that to the extent it placed a burden on TKT the district court committed error. However, we hold this error to be, for the most part, harmless. After analyzing enablement and apparently finding the relevant unclaimed disclosures of Sugimoto nonenabled, the court nevertheless conducted a full anticipation analysis. Indeed, the district court performed a detailed analysis of each piece of anticipating prior art—including Sugimoto—asserted against each of Amgen's claims. *Id.* at 109-10, 57 USPQ2d at 1477. From this analysis the court found that "none of the cited references disclose [sic] each and every limitation of

any of Amgen's individual claims." *Id.* at 109, 57 USPQ2d at 1477. It does not appear that TKT has argued this alternative finding was clear error. However, we do not rest on waiver, but affirm the district court's finding that Sugimoto does not anticipate any asserted claims of the '080, '349, or '698 patents because from our review of the evidence and the subsidiary finding of the court, it was not clear error to find in each claim one or more limitations not disclosed in Sugimoto. But given our earlier holdings, we must vacate and remand the finding that Sugimoto does not anticipate claim 1 of the '422 patent. On remand, the district court should consider whether claim 1 of the '422 patent is novel over Sugimoto in light of the court's new definition of "therapeutically effective" and while mindful of the principle that source limitations cannot impart novelty to old compositions.

Our review is not yet finished, however, because it is apparent from the district court's opinion that TKT relied upon Sugimoto to assert invalidity of the patents in suit under both § 102 and § 103. In its obviousness inquiry, the district court disregarded Sugimoto because it concluded it was not enabled. It recognized, however, the important and potentially dispositive role that Sugimoto would have otherwise played in the obviousness analysis:

> Had the court concluded otherwise [*i.e.*, that Sugimoto was enabled], the Sugimoto patent would go a long way toward proving TKT's obviousness defense. As explained above, Sugimoto disclosed EPO-producing fused cells and advised that (1) conventional techniques can be utilized to achieve purification and (2) the human EPO produced thereby can be used in pharmaceutical compositions for the treatment of anemia. Thus, the patent itself suggested combining its invention with prior art sources relating to both purification and therapeutic delivery. Provided that one of ordinary skill in the art could actually make the EPO-producing cells described

> in the Sugimoto patent, a point on which TKT failed to persuade this court, such a combination of prior art materials might render invalid the pharmaceutical composition claims of the '933, '080, and '422 patents.

Id. at 114 n.29, 57 USPQ2d at 1480 n.29. Under § 103, however, a reference need not be enabled; it qualifies as a prior art, regardless, for whatever is disclosed therein. See *Symbol Tech., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1578, 19 USPQ2d 1241, 1247 (Fed. Cir. 1991); *Reading & Bates Constr. Co. v. Baker Energy*, 748 F.2d 645, 652, 223 USPQ 1168, 1173 (Fed. Cir. 1984). Therefore, the district court's obviousness holdings with respect to Sugimoto are vacated and remanded. On remand, the district court should reconsider obviousness with respect to Sugimoto, but should do so without reference to whether Sugimoto is enabled, as enablement of the prior art is not a requirement to prove invalidity under § 103.

V

The last issue on appeal is inequitable conduct. TKT raised before the district court essentially three instances of allegedly inequitable activities by the patentee: withholding crucial details regarding the Goldwasser study; withholding certain results of its own experiments that undermined the validity of the '933 patent; and failing to disclose to the Patent and Trademark Office the existence of this litigation. The district court found that TKT had not proven inequitable conduct by clear and convincing evidence, and we have not been persuaded on appeal that a contrary result is compelled. In reaching this conclusion, we need look no further than the district court's determination that TKT's case was doomed because it was bereft of evidence of intentional deception:

> TKT has failed to produce any persuasive evidence that causes the Court to doubt the integrity of the individuals who bore the duty of shepherding the Amgen patent applications through the Patent and Trademark Office,

> [so] its charge of inequitable conduct utterly fails . . . . TKT has failed to prove by clear and convincing evidence that this [experimental] data was material or that it was withheld with intent to deceive . . . . [And] TKT has not even begun to demonstrate that Amgen representatives possessed an intent to deceive the [PTO] in failing to provide specific notification regarding this litigation . . . . In summary, TKT's proof of inequitable conduct with respect to each of these charges falls short of the mark. Although the directness of Amgen's disclosures varies depending on the particular piece of disputed information, one truth remains the same throughout: Amgen's representatives never intended to deceive the Patent Office. Consequently, a finding of inequitable conduct would be error and the Court does not so find on the complete record.

Id. at 141, 145, 147, 57 USPQ2d at 1500, 1504, 1505.

A patent applicant commits inequitable conduct when, during prosecution of the application, he makes an affirmative representation of a material fact, fails to disclose material information, or submits false material information, and does so with the intent to deceive. *Refac Int'l, Ltd. v. Lotus Dev. Corp.*, 81 F.3d 1576, 1581, 38 USPQ2d 1665, 1669 (Fed. Cir. 1996). As a general principle, materiality and intent are balanced—a lesser quantum of evidence of intent is necessary when the omission or misrepresentation is highly material, and vice versa *See, e.g., GFI, Inc. v. Franklin Corp.*, 265 F.3d 1268, 1273, 60 USPQ2d 1141, 1143 (Fed. Cir. 2001). At the same time, however, there must be some threshold showing of intent to be balanced; we will not find inequitable conduct on an evidentiary record that is completely devoid of evidence of the patentee's intent to deceive the PTO. *See Allen Eng'g Corp. v. Bartell Indus., Inc.*, No. 01-1238, 2002 U.S. App. LEXIS 15418, at *33 (Fed. Cir. Aug. 1, 2002) ("Materiality does not presume intent, which is a separate and essential component of inequitable conduct."

(quoting *Allen Organ Co. v. Kimball Int'l, Inc.*, 839 F.2d 1556, 1567, 5 USPQ2d 1769, 1778 (Fed. Cir. 1988))).

Here, the district court determined that there was no evidence of intent to deceive, and TKT has directed us to none on appeal. Thus, to conclude the Amgen patents are unenforceable—as TKT requests—we must conclude (1) that the district court clearly erred by failing to find the minimal requisite intent to deceive, and (2) that it abused its discretion in weighing the degree of materiality against the degree of deceptive intent and by not then rendering the patents unenforceable. On the record before us, we decline to do so.

CONCLUSION

We summarize our decision as follows. Affirmed are: the district court's claim construction; its finding that all of the patents in suit are enforceable; its finding that the '933 patent is invalid; and its finding that the '349 (product claims only) and the '422 patents are infringed. We vacate: its finding that the '933 patent was not infringed; several of its validity findings with respect to the '080, the '349, the '422, and the '698 patents; and its infringement findings with respect to the '698 patent and '349 patent claim 7. On remand, the district court should: construe the claim term "therapeutically effective" and then reconsider validity under §§ 102 and 103 in view of Goldwasser; reconsider validity of all asserted claims under § 103 and claim 1 of the '422 patent under § 102 in view of Sugimoto, with Amgen bearing the burden of proof on its non-enablement (for § 102 purposes only); reassess infringement of the accused method by comparing it solely to the limitations of each of the asserted method claims; and reevaluate its finding of infringement under the doctrine of equivalents of the '080 patent, focusing on the application of prosecution history estoppel.

AFFIRMED IN PART, VACATED IN PART, REMANDED. No costs.

CLEVENGER, *Circuit Judge,* dissenting in part.

I join my colleagues' thorough opinion in all respects save one, albeit significant, exception. Because the claims lack meaningful limitations on the structure of the erythropoietin-producing cells, I cannot agree that the district court should have abstained from inquiring fully whether the claims were suspect under the enablement and written description provisions of 35 U.S.C. § 112, ¶ 1.

As described by the specifications of the patents in suit, Amgen in 1984 cloned and sequenced the DNA encoding human erythropoietin (EPO). Amgen then showed that by introducing the cloned EPO DNA (linked to a promoter sequence) into mammalian cells, those cells could be engineered to express high levels of functional human EPO protein. The parties refer to this as "exogenous DNA" expression of EPO. Amgen obtained several patents that cover the use and manipulation of cloned EPO DNA, and these patents, battle-tested through litigation, have been the foundation of Amgen's successful business of manufacturing and selling recombinant EPO. But these patents are not in suit here, and TKT's method for producing EPO does not rely upon manipulation of cloned EPO DNA or "exogenous DNA" expression technology.

The claims in suit here contain no significant limitations as to how the recombinant EPO is expressed, or as to the structure of the EPO-producing cells, so long as the EPO is "non-naturally occurring" or produced in "vertebrate cells." The central question in this case is therefore whether Amgen's disclosure of one means of producing synthetic EPO in mammalian cells, namely exogenous DNA expression, entitles it to claim all EPO produced by mammalian cells in culture, or all cultured vertebrate cells that produce EPO. I think this is a question of some importance. Yet it is a question that the district court simply refused to consider. Although the district court admitted that Amgen's disclosure

was limited to exogenous DNA expression, the district court quite clearly and explicitly refused to decide whether the absence of any exogenous DNA limitations rendered the asserted claims vulnerable to the enablement challenge mounted by TKT under section 112. According to the district court, because the asserted claims were to "compositions" rather than "processes," "the specification need teach only one mode of making and using a claimed composition." *Amgen Inc. v Hoescht Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 160, 57 USPQ2d 1449, 1515 (D. Mass. 2001). *See also id.* at 160, 164 n.57, 57 USPQ2d at 1516, 1518 n.57. Likewise, the district court refused to inquire whether the absence of limitations on the means of EPO expression raised questions of compliance with the written description requirement, holding that such an inquiry was irrelevant to composition claims. *Id.* at 150-51, 57 USPQ2d at 1508.

With respect to the '080 and '422 patents, which claim "non-naturally occurring" EPO and EPO "purified from mammalian cells grown in culture," the majority, like the district court, essentially passes over the question of whether these limitations—which are essential for patentability of the claims—raise issues of compliance with the enablement and written description requirements of section 112. The majority holds that patentees are free to decorate their composition claims with source and process limitations without any concern for whether the full scope of those limitations is enabled or described, and that these requirements of section 112 are waived so long as the patentee succeeds in characterizing its claims as "product" claims. Competent patent attorneys should be quick to take advantage of the majority's broad exemption from the disclosure requirements by the appropriate phraseology. Rather than endorse the district court's elevation of form over substance, I would vacate its decision on these issues regarding the '080 and '422 patents, and remand for further consideration in light of the vast scope of

the claims in suit for which there appears to be insufficient enabling disclosure or written description.

With particular reference to the '349 patent, which claims not EPO polypeptides but the cells that produce them, I think the district court's abstention from scrutiny under section 112 is even more patent error. The majority focuses on the district court's findings that the invention could readily be practiced in mammalian or vertebrate cells other than the hamster and monkey cells taught by the specification. I agree that TKT has not shown error in these findings. But, as it did for the EPO claims, the district court simply refused to consider whether the absence of any exogenous DNA limitations raised enablement issues, "[b]ecause Amgen is only required to enable skilled artisans to make its claimed product by only one method . . . ." *Id.* at 164 n.57, 57 USPQ2d at 1518 n.57. For the EPO-secreting cells, the absence of an exogenous DNA limitation is not a failure to limit how the product is made, but a failure to limit the structure of the claimed product itself. A cell, as employed in the patents in suit, is nothing more than a biological machine for making EPO. Even in more predictable arts, one who is first to make a machine is not entitled as a matter of law to claim any or all machines so long as they perform the same function. I would think it uncontroversial that even one who is first to make polymer X or alloy Y cannot obtain a claim as broad as "A machine that makes polymer X," or "A process that yields alloy Y," without reciting additional limitations that define the structure of the claimed machine or the steps necessary to carry out the claimed process.

Yet that is exactly what the district court and the majority allow the '349 patent to achieve. It claims any or all cultured vertebrate cells that can secrete a defined amount of EPO, with only a single limitation on their structure: that they "compris[e] non-human DNA sequences which control transcription of DNA encoding human erythropoietin," or that

they "comprise transcription control DNA sequences, other than human erythropoietin transcription control sequences, for production of human erythropoietin." This is little more precise than a recitation of "A machine that makes polymer X, wherein the machine comprises means for controlling how much polymer X is made." The specification teaches only a single means by which the use of a transcription control sequence can coax a vertebrate cell to secrete EPO: by transforming that cell with an exogenous expression vector on which the transcription control sequence is linked to cloned EPO DNA. Yet the claims leave this essential aspect of the invention undefined. It is black-letter law that claims failing to recite a necessary element of the invention fail for lack of an enabling disclosure, *In re Mayhew*, 527 F.2d 1229, 1233, 188 USPQ 356, 358 (CCPA 1976), and that disclosure of one or two species may not enable a broad genus under these circumstances. *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1444-45 (Fed. Cir. 1991). At the very least, the absence of structural limitations in the '349 patent raises questions of its enablement, and I cannot agree that the district court chose correctly by ignoring those questions altogether. We should vacate the district court's judgment that the '349 patent passes enablement muster, and require the court to apply the correct law to the plain facts.

I must also disagree with the majority that the district court's approach was faithful to this court's articulation of the written description requirement of section 112, as expressed in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 45 USPQ2d 1498 (Fed. Cir. 1998). *Eli Lilly* articulated two principles of the written description requirement: that *in haec verba* description of broadly described generic subject matter may not suffice to describe the subject matter of that particular claim, 119 F.3d at 1567, 43 USPQ2d at 1404-05, and that disclosure of a species may not suffice to describe a genus, *id.*

at 1568-69, 43 USPQ2d at 1405-06. The district court followed neither of these principles here, and the majority, dismissing *Eli Lilly* on the grounds that no undisclosed DNA molecule appears in this case, verges on confining *Eli Lilly* to its facts.

Nor am I convinced that the district court's approach was faithful to *Gentry Gallery*. In *Gentry*, only those claims that included limitations such as "wherein the control means are located on the console" satisfied the written description requirement. Because the specification failed to disclose any location for the controls other than on the console, those claims that lacked such limitations were invalid under § 112, ¶ 1. 134 F.3d at 1479-80, 45 USPQ2d at 1503-04. The question here is similar: whether the claims fail the written description requirement for lack of "exogenous DNA" limitations, because the specification discloses only the exogenous DNA technology that was state of the art in 1984.

Even if we ignore the patents' statement that the claimed EPO molecules are "uniquely characterized by being the product of . . . expression . . . of exogenous DNA sequences" (which of course we cannot), I think the parallels between this case and *Gentry Gallery* are inescapable. The invalid claims in *Gentry* recited elements that could readily be found in the text of the specification (a couch, controls, a console), but those claims nonetheless failed the written description requirement because they included no limitations on how those elements were *arranged*. Likewise, the '349 claims—for which I think it must be conceded that structure of the EPO-secreting cell is a relevant question—recite particular elements found in the specification (cells, non-human control sequences, EPO-coding DNA), but do not include limitations on the arrangement of those elements, *e.g.* that the non-human control sequences and coding DNA are present on an exogenous expression vector in the cell. I agree that as a matter of claim interpretation there is no justification for

importing an "exogenous DNA" limitation into the claims. But the absence of such limitations must weigh heavily in the section 112 inquiry, else we hold that claims become more resistant to written description challenges the more broadly drafted they are.

While I share my colleagues' admiration for the considerable efforts of the district court in this complicated case, I cannot share their faith that the district court properly and conscientiously applied *Eli Lilly* and *Gentry Gallery*, when the district court's opinion is completely devoid of reference either to those cases or to the principles they espouse. If the district court did not focus on the correct law to be applied, then its factual findings merit no deference, and the correct remedy for this omission is to vacate the district court's judgment on this point and remand for further consideration. Our precedent has little value if the district courts may overlook its certain pertinence, if not its plain applicability.

APPENDIX E

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

CIVIL ACTION NO. 97-10814-WGY

AMGEN, INC.,

Plaintiff,

v.

HOECHST MARION ROUSSEL, INC. and
TRANSKARYOTIC THERAPIES, INC.,

Defendants.

FINDINGS, RULINGS, AND ORDER

YOUNG, C.J. January 19, 2001

In this jury waived declaratory judgment action, Amgen, Inc. ("Amgen") seeks a declaration that certain of the patents protecting its best selling drug EPOGEN® are infringed by the conduct of the defendants, Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc. (collectively "TKT"). TKT denies infringement and, in turn, counterclaims that Amgen's patents are invalid on a number of grounds.

Amgen, the first to discover and manufacture a recombinant DNA product similar to natural erythropoietin ("EPO") and useful in various medical treatments, has reaped significant commercial rewards from its discoveries, *see* Patricia Van Arnum, *Active Pharmaceutical Ingredients: The Opportunities in the Branded Prescription Market*, Chemical Market Rep., Oct. 30, 2000, WL 10/30/00 CHEMMKT REP FR 14 (noting that Amgen's Epogen had sales of $1.76 billion in 1999); Vicki Brower, *Amgen Comes Out on Top in Blood Drug Patent Tussle*, Biotechnology Newswatch, Jan. 4, 1999, WL 1/4/99 BIOTECHNW 1 (noting that EPO was then

the "biggest-selling biotechnology drug ever developed" and that Amgen's EPO sales accounted for over fifty percent of its 1997 $2.4 billion revenue). As one would expect, Amgen has sought to preserve its commercial success through a cluster of related patents that it has defended with skill and perseverance.[1]

In conjunction with Hoechst Marion Roussel, Inc., now known as Aventis Pharmaceuticals, Inc., TKT, a smaller company, seeks to capitalize upon apparent advances in genetic engineering by targeting the most lucrative commercial recombinant DNA products and designing around them. *See* Trial Tr. at 1772:21 to 1773:2, 1786:5 to 1787:7. It, too, as one might expect, is no stranger to litigation.[2] The present

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[1] *See, e.g., Amgen, Inc.* v. *Elanex Pharm., Inc.*, No. C93-1483D, 1996 WL 84590 (W.D. Wash. Feb. 6, 1996); *Amgen, Inc.* v. *Genetics Inst., Inc.*, 877 F. Supp. 45 (D. Mass. 1995), *aff'd*, 98 F.3d 1328 (Fed. Cir. 1996); *Amgen, Inc.* v. *Chugai Pharm. C., Ltd.*, No. 87-2617-Y, 1989 WL 169006 (D. Mass. Dec. 11, 1989), *aff'd in part, vacated in part*, 927 F.2d 1200 (Fed. Cir. 1989), *cert. denied*, 502 U.S. 856 (1991); *Ortho Pharm. Corp.* v. *Amgen, Inc.*, 709 F. Supp. 504 (D. Del.), *vacated in part*, 882 F.2d 806 (3d Cir.), *appeal after remand*, 887 F.2d 460 (3d Cir. 1989); *Amgen, Inc.* v. *Chugai Pharm. Co., Ltd.*, 706 F. Supp. 94 (D. Mass. 1989); *Fritsch* v. *Lin*, 21 U.S.P.Q.2d (BNA) 1731 (Bd. Pat. App. & Interf. 1991); *Fritsch* v. *Lin*, 21 U.S.P.Q.2d (BNA) 1737 (Bd. Pat. App. & Interf. 1991); *Fritsch* v. *Lin*, 21 U.S.P.Q.2d (BNA) 1739 (Bd. Pat. App. & Interf. 1991); *In the Matter of Certain Recombinant Erythropoietin*, 10 U.S.P.Q.2d (BNA) 1906 (U.S. Intl Trade Comm'n 1989), *vacated*, *Amgen, Inc.* v. *United States Intl. Trade Comm'n*, 902 F.2d 1532 (Fed. Cir. 1990).

[2] *See Amgen, Inc.* v. *Hoechst Marion Roussel*, 190 F.R.D. 287 (D. Mass.), *aff'd*, 232 F.3d 905, 2000 WL 290346 (Fed. Cir. 2000) (un-published decision); *Aetna U.S. Healthcare, Inc.* v. *Hoechst Aktiengesellschaft*, 54 F. Supp.2d 1042, *reconsid. denied*, 67 F. Supp. 2d 1242 (D. Kan. 1999); *Biovil Corp. Int'l* v. *Hoechst Aktiengesellschaft*, 49 F. Supp. 2d 750 (D.N.J. 1999); *Aetna U.S. Healthcare, Inc.* v. *Hoechst Aktiengesellschaft*, 48 F. Supp. 2d 37 (D.D.C. 1999); *Eli Lilly & Co.* v. *Roussel Corp.*, 23 F. Supp. 2d 460 (D.N.J. 1998); *Mut. Pharm. Vo., Inc.* v. *Hoechst Marion Roussel, Inc.*, 46 U.S.P.Q.2d (BNA.) 1148 (E.D Pa. 1997); *Hoechst Marion Roussel, Inc.* v. *Scherinq-Plough Corp.*, No. 97-

litigation, in fact, has been brewing for some time, *see Amgen, Inc* v. *Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104 (D. Mass. 1998), and when it ultimately erupted in June of 1999, the parties were ready.

As an aside, it is only just to note that this case has been presented with high integrity, an unswerving fidelity to court rules and procedures, and a consummate excellence in trial practice that makes it a model not only for the intellectual property bar, but for lawyers everywhere. Any failings in understanding are mine, and mine alone.

The course of the litigation may be briefly sketched.

Early on, the parties agreed on a list of experts upon whom the Court might call for technical assistance. The Court chose Professor Chris Kaiser of the Massachusetts Institute of Technology from this list, and has met privately with him for background tutorial assistance.[3]

0147-CV-W-5, 1997 WL 79796 (W.D. Mo. Feb. 10, 1997); *Hoechst Marion Roussel, Inc.* v. *Par Pharm. Inc.*, 39 U.S.P.Q.2d (BNA) 1363 (D.N.J. 1996).

[3] While not in any way original to this Court, the use of and protocol followed by the Court with technical advisors is extensively discussed in *MediaCom Corp.* v. *Rates Tech., Inc.*, 4 F. Supp. 2d 17, 29-30 (D. Mass. 1998) (tracing Judge Richard Stearns' technique of using technical advisors in *Biogen, Inc.* v. *Amgen, Inc.*, No. 95-10496-RGS [D. Mass. Dec. 10, 1996]). As this Court remarked in *MediaCom*, the technique employed by Judge Stearns is extraordinarily helpful to any judge faced by complex technical litigation. Not surprisingly, the use of technical advisors has received favorable comment locally, *see* Richard Stearns' Remarks at the Massachusetts Continuing Legal Education's Federal Judicial Forum (Oct. 16, 2000) (attributing the original idea to Judge Charles Wyzanski in *United States* v. *United Shoe Machinery Co.*, 223 F. Supp. 826 [D. Mass. 1963]), nationally, *see* Sandy Choi, *A Perspective on Patent Claim Construction After* Markman v. Westview, in *Federal Courts, Judicial Forum 2000,* at 392 (William G. Young ed. 2000), and even internationally, *see* Shinichi Yoshikawa & Aya Takahashi, *The Use of Experts in the Pre-trial Stage of Civil Litigation that Concerns*

Towards the close of discovery, Amgen moved for summary judgment on the issue of infringement.[4] This motion necessitated construction of the patent claims, and the Court held a *Markman* hearing on March 27, March 28, and April 10, 2000. Thereafter, the Court granted summary judgment to Amgen on a particular claim in one of the five patents in issue. The motion for summary judgment was otherwise denied.

Trial commenced on May 15, 2000 and continued for twenty-three days spread over four months.[5] At the close of Amgen's case in chief, the Court held, pursuant to Fed. R. Civ. P. 52(c), that TKT had not infringed the process claims of Amgen's U.S. Patent No. 5,618,698 (issued Apr. 8, 1997). Trial concluded on September 8, 2000, and the matter was taken under advisement.

Technical Issues—Technical Advisors in Markman *Hearings in Patent Litigation in the United States*, 104 Law J. Legal Training & Res. Inst. 67 (2000). Under an imaginative program sponsored by the Supreme Court of Japan, Judge Yoshikawa of the Osaka District Court and Judge Takahashi of the Tokyo District Court actually sat with this Court during the trial and post-trial consideration of this case.

In one respect, the Court refined the protocol discussed in *MediaCom*. In this case, every contact with Professor Kaiser has been made a matter of record. While this record remains sealed, it is, of course, available to any appellate court should it so require.

[4] A motion for summary judgment is, of course, an excellent vehicle to frame the essential questions of patent claim construction. *See MediaCom*, 4 F. Supp. 2d at 22-23. Moreover, the timing of the *Markman* hearing in this case was optimal. *See MacNeill Eng'g Co.* v. *Trisport, Ltd.*, No. 98-12019, slip op. at 7 (D. Mass. Jan. 10, 2001).

[5] One curious aspect of this case illustrates perfectly the utterly speculative nature of the stock market during the Spring and Summer of 2000. Each day of trial, the courtroom would fill with the financial press, financial analysts and their hangers-on, and lawyer commentators. Each day at the morning break (10:45 a.m.) and the luncheon recess (1:00 p.m.), this group would debark into the hallway, activate their cell phones,

I. THE PATENTS AT ISSUE

There are five patents at issue in this case: U.S. Patent No. 5,547,933 (issued Aug. 20, 1996) ("'933 patent"), Trial Ex. 2; U.S. Patent No. 5,618,698 (issued Apr. 8, 1997) ("'698 patent"), Trial Ex. 4; U.S. Patent No. 5,621,080 (issued Apr. 15, 1997) ("'080 patent"), Trial Ex. 3; U.S. Patent No. 5,756,349 (issued May 26, 1998) ("'349 patent"), Trial Ex. 5;

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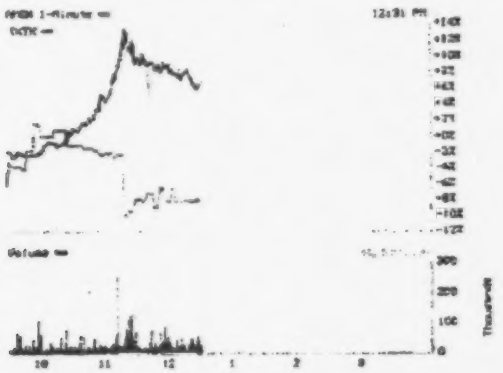
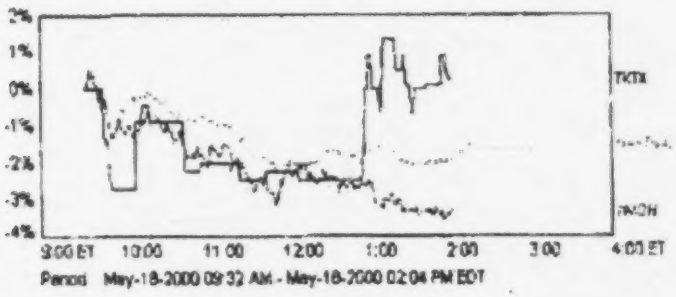
and shortly thereafter the publicly-traded stocks of the litigants would bob or dip in response to some random comment by the Court, the trial lawyers, or a particular witness. The two charts below, from April 26 and May 18, 2000 respectively, illustrate the speculative phenomenon.



Interactive Charting for Amgen, Inc., *at* http://www.marketwatch.com (last visited Apr. 26, 2000).



[S] = stock split or spinoff

Amgen's MASDAQ Quote, *at* http://www.quicken.com (last visited May 18, 2000).

and U.S Patent No. 5,955,422 (issued Sept. 21, 1999) ("'422 patent"), Trial Ex. 6.

All of these patents share a common disclosure and identical specifications. Trial Exs. 2-6. Only the claims differ. Each of the patents claim priority from the following common applications: U.S. Patent Application Serial No. 675,298 (Nov. 30, 1984), which is a continuation-in-part of U.S. Patent Application Serial No. 655,841 (Sept. 28, 1984), which is a continuation-in-part of U.S. Patent Application Serial No. 582,185 (Feb. 21, 1984), which is a continuation-in-part of U.S. Patent Application Serial No. 561,024 (Dec. 13, 1983). Trial Exs. 2-6.

II. "THE NAME OF THE GAME IS THE CLAIM":[6] CLAIM CONSTRUCTION

It is appropriate to pause for a moment to emphasize the particular procedural approach that this Court used in conducting the *Markman* hearing. District courts have differed significantly in the timing and procedure for *Markman* hearings—some engaging in claim construction prior to trial and others after hearing all of the evidence at trial. *See* William F. Lee & Anita K. Krug, *Still Adjusting to Markman: A Prescription for the Timing of Claim Construction Hearings*, 13 Harv. J.L. & Tech. 55, 73 (1999). I have consistently taken the procedural approach of conducting the *Markman* hearing at the summary judgment stage of litigation or at the point when discovery has closed and trial is approaching. *See, e.g.*, *MacNeill Eng'g Co.* v. *Trisport, Ltd.*, No. 98-12019, slip op.

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[6] Giles S. Rich, *Extent of Protection and Interpretation of Claims—American Perspectives*, 21 Int'l Rev. Indus. Prop. & Copyright L. 497, 499 (1990); *see* T. Whitley Chandler, *Prosecution History Estoppel, the Doctrine of Equivalents, and the Scope of Patents*, 13 Harv. J.L. & Tech. 465, 479 (2000) ("Every patent decision today first pays homage to the exalted status of the *claims*. Why? Because the right to exclude does not turn on what was invented, but what is *claimed*.") (footnote omitted).

at 7 (D. Mass. Jan. 10, 2001); *MediaCom*, 4 F. Supp. 2d at 22-23. I have taken care to note that the benefits of so doing range from constitutional concerns arising from conducting such a hearing too soon to efficiency concerns arising from conducting the hearing too late. *See MediaCom*, 4 F. Supp. 2d at 22; Lee & Krug, *supra* at 82-85.

Here, however, I want more specifically to emphasize that when the *Markman* hearing is conducted at the summary judgment stage, it is also important to conduct the two hearings independently of each other—the *Markman* hearing being held prior to and entirely independently of the summary judgment hearing. This is exactly the procedure that the Court followed in the case at hand, although other courts have chosen to address the issues raised with respect to claim construction in the context of the motion for summary judgment and hence conduct the *Markman* hearing in conjunction with the hearings on summary judgment, *see, e.g.*, *Biogen* v. *Berlex Labs., Inc.*, 113 F. Supp. 2d 77, 81 (D. Mass. 2000) (conducting the *Markman* hearing "in connection with" the summary judgment hearings).

This Court's *Markman* procedure turns on what this Court sees as the crucial distinction between construing patent claims in the *context* of considering motions for summary judgment as opposed to construing the patent claims *without regard* to the alleged infringement issue presented in the summary judgment motion. With this distinction in mind, this Court scrupulously kept the issues separate in order to avoid conflating the legal explication required by *Markman* with the fact finding that the Seventh Amendment ultimately reserves for the American jury. *See Ciulla* v. *Rigny*, 89 F. Supp. 2d 97, 101, 102 & n.7 (D. Mass. 2000) (discussing the constitutional and communitarian values strengthened by jury fact finding)

Although, under current law, both approaches are permitted in the wake of *Markman*, just as the Federal Circuit has spoken to the question of what evidence a court should

consider in a *Markman* hearing, *Vitronics Corp.* v. *Conceptronic, Inc.*, 90 F.3d 1576, 1582-83 (Fed. Cir. 1996), perhaps it ought similarly fashion flexible procedural boundaries within which to conduct such a hearing. Failure to do so not only deprives litigants of the benefit of consistent treatment among districts (or even among specific judges), but also risks descending a slippery slope toward the erosion of the role of the fact finder in patent litigation.

This latter fear is the central concern of this Court with the procedural approach to *Markman* hearings that mixes issues of claim construction with that of infringement by simultaneously considering factual evidence of each. I concede that, analytically, such mixing ought not affect the outcome of claim construction. Nonetheless, I fear that such mixing cuts against the spirit of both *Markman* itself and its recognition of the importance of the fundamental divide between fact and law (and consequently, fact finder and law definer) upon which our legal system is based because it openly invites the risk that issues of fact and law will be conflated.[7] Indeed, to limit procedurally the consideration of factual issues at the *Markman* hearing is analogous to the Federal Circuit's own warning against the consideration of extrinsic evidence where intrinsic evidence alone will adequately allow for definition of the disputed claim term. *See Vitronics Corp.*, 90 F.3d at 1583.

Judges are expected to be objective and analytic in their role as law definer, and I daily seek to meet this standard. Moreover, I do not even mean to suggest that the outcome of this case would have somehow been different had this Court followed the approach that other courts apply and mixed the

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[7] Of course, mixing the *Markman* hearing with the court's consideration of summary judgment merely creates such a risk. Careful parsing of the issues can avoid this risk of conflating fact and law. *See Biogen*, 113 F. Supp. 2d at 101 (court stated explicitly in its claim construction that it did not rely on extrinsic evidence of invalidity in construing the claims).

questions of claim construction into the hearing on summary judgment. But the risk that this procedure creates of conflating issues of fact and law is simply too high in my eyes. Let us not forget that the Seventh Amendment requires that infringement cases be tried to a jury. *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370, 377 (1996). The judiciary has recently mandated other procedural hurdles that seem to fly in the face of efficiency in the sole effort to preserve the role of the American jury. *See Apprendi* v. *New Jersey*, 530 U.S. 466 (2000). Believing in the benefits of such a simple prophylactic measure—considering claim construction without regard to infringement—I made careful efforts to follow this procedure consistently. The result is an honest effort to give meaning to the true spirit of *Markman* and the due consideration that it gave to the role of the jury in patent litigation.

During the three-day *Markman* hearing, the Court entertained oral argument from counsel for each party with respect to ten claim terms that were pre-selected due to their relationship to disputed issues arising in Amgen's pending summary judgment motion. Counsel referred the Court to relevant portions of the specification as well as the prosecution history. Demonstrative exhibits were utilized, but evidence was neither offered nor admitted. After hearing each party's presentation, the Court announced its constructions.

During the course of the *Markman* hearing, the positions of each party remained generally consistent. On the one hand, Amgen consistently advocated what the Court referred to as the "ordinary meaning" of a particular claim term. On the other hand, TKT often sought to insert a limitation by arguing that without such limitation, the claim would be invalid for lack of adequate description or enablement. Their positions, of course, were not surprising. As the patent holder, Amgen had every incentive to persuade the Court to adopt the broadest possible interpretation in order to sweep within its

patents' span the greatest possible amount of its competitors' activities. TKT meanwhile proffered limiting interpretations with an eye toward distinguishing its products and process from the scope of the patents' language. This dance is well known.[8] Both parties cite Federal Circuit case law that appears to support their conflicting views, thus creating the impression that the case law itself is contradictory. A close examination of this case law, however, reveals that TKT's approach—though accepted in some limited circumstances—is inappropriate here.

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[8] These well known strategies for claim construction have, in fact, reached the point of ridicule in the patent subculture as this inciteful poem (to be sung to the tune of "Camelot") exemplifies:

A law was made 200 years ago here
Grant patents, help promote inventive thought
Today the system's thriving and our credo
Is claim-a-lot

We push the envelope,
expand the boundaries
Create a circle from a tiny dot
Our product's forged with words
and not in foundries
We claim a lot

(Bum bum, etc.)

Claim-a-lot (claim-a-lot)
I know it sounds a bit bizarre
Lord, we claim-a-lot (oh yes, we claim-a-lot)
Stretch out those claims so far

Though prior art may set some limitations
Restricts our flights of fancy, clever thought
Our efforts, not for naught
Results, so boldly wrought
Construct our patent juggernauts
By claiming quite a lot.

Kramer, Levin, Naftalis & Frankel LLP, *Claim-a-Lot*, *in* Pamphlet for N.Y. Intellectual Property Law Association 78th Annual Dinner (Mar. 24, 2000).

In many instances, Amgen relied primarily on the familiar notion that "[f]irst, and most importantly, the language of the claim defines the scope of the protected invention." *Bell Communications Research, Inc.* v. *Vatalink Communications Corp.*, 55 F.3d 615, 619 (Fed. Cir. 1995); *see also Renishaw Plc* v. *Marposs Societa' Per Azioni*, 158 F.3d 1243, 1248 (Fed. Cir. 1998) ("[T]he claim construction inquiry, therefore, begins and ends in all cases with the actual words of the claim. [T]he resulting claim interpretation must, in the end, accord with the words chosen by the patentee to stake out the boundary of the claimed property."); *Abtox, Inc.* v. *Exitron Corp.*, 122 F.3d 1019, 1023 (Fed. Cir. 1997) ("[T]he language of the claim frames and ultimately resolves all issues of claim interpretation."). Relatedly, absent a clear and specific statement in the patent specification giving a claim term a special definition, the Court must adopt the plain and ordinary meaning given by persons experienced in the field of the invention. *See Renishaw*, 158 F.3d at 1249; *Hoechst Celanese Corp.* v. *BP Chems. Ltd.*, 78 F.3d 1575, 1578 (Fed. Cir. 1996); *see also Digital Biometrics, Inc.* v. *Identix, Inc.*, 149 F.3d 1335, 1344 (Fed. Cir. 1998) (patentee may be her own lexicographer). Adhering to these cardinal principles of claim construction, this Court discharges its duty of claim construction by interpreting the claim terms pursuant to the plain and ordinary meaning ascribed to them by one skilled in the art.

Derived from these core principles is the additional canon of claim construction that a court may not read a limitation into a claim from the written description, but may look to the written description to define a term already in a claim limitation, for a claim must be read in light of the specification. *Vitronics Corp.*, 90 F.3d at 1582. Thus, even when the Court looks at intrinsic evidence to assist it in identifying the meaning of a claim term, the words of the claim should still be given their preeminence. This canon creates a fine but important line for the Court to walk: "It is entirely proper to use the specification to interpret what the patentee meant by a

word or a phrase in the claim. But this is not to be confused with adding an extraneous limitation appearing in the specification, which is improper." *E.I. du Pont De Nemours & Co.* v. *Phillips Petroleum Co.*, 849 F.2d 1430, 1433 (Fed. Cir. 1988) (citation omitted); *see generally* David C. Radulescu, *The Federal Circuit's Narrowing of the Literal Scope of Patent Claims by Focusing on Embodiments Disclosed in the Specification*, 82 J. Pat. & Trademark Off. Soc'y 59 (2000). To ensure that a litigant does not improperly cross this line, a party wishing to use statements in the written description to confine a patent's scope must first point to a term in the claim with which to incorporate those statements. *Renishaw*, 158 F.3d at 1248. "Without any [such] claim term that is susceptible of clarification by the written description, there is no legitimate way to narrow the property right." *Id.* Under such circumstances, use of the specifications to "define" the claim term would impermissibly cross over the line by using the specifications to add extraneous limits on the patent.[9]

In contrast, TKT relies most heavily upon a number of Federal Circuit cases standing for the proposition that claims ought be construed so as to sustain their validity. *See, e.g.*, *Wang Labs.* v. *Am. Online, Inc.*, 197 F.3d 1377, 1383 (Fed. Cir. 1999). During the claim construction phase of the case,

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[9] The line between interpreting claim language in light of the specification and adding an extraneous limitation from the specification is relevant in other canons of construction. As will be seen, the doctrine upon which TKT relied that claims ought be construed so as to sustain their validity should be subject to the same restriction. Thus, although the Federal Circuit has stated that "if the claim is susceptible to a broader and a narrower meaning, and the narrower one is clearly supported by the intrinsic evidence while the broader one raises questions of enablement under § 112, ¶ 1, we will adopt the narrower of the two," *Digital Biometrics*, 149 F.3d at 1344, this is nonetheless subject to the limitation that the party seeking to incorporate a limitation by relying on the specification must first identify a claim term hook susceptible of the narrower meaning upon which to hang the limitation.

counsel for TKT implored the Court to reject Amgen's proffered interpretations because such broad interpretations were not adequately disclosed in the patents' specification. In short, TKT argued that while Amgen taught the production of EPO using a precise process and specific cells, Amgen went on to claim far beyond its teachings. Thus, if the Court adopted a claim construction commensurate with the plain and ordinary meaning of the overbroad claim terms, its construction would run counter to the Federal Circuit's command that claims be construed so as to sustain their validity..

Indeed, incorporating validity concerns during claim construction may apply "where there are several common meanings for a claim term" and thus "the patent disclosure serves to point away from the improper meanings and toward the proper meaning." *Renishaw*, 158 F.3d at 1250. In this sense, the canon that claim terms ought be construed to sustain their validity is simply an interpretation tool to aid courts in determining what a reasonably disputed claim term means in light of the specifications. The Federal Circuit has warned, however, that the canon that claims ought be interpreted to sustain their validity is not without limits:

> The [Supreme] Court has consistently limited the axiom [that claims should be interpreted to preserve their validity] to cases where the construction is "practicable" and does not conflict with the explicit language of the claim. [The Federal Circuit also has] consistently employed the caveat, "if possible," to our instruction that claims should be construed to sustain their validity. We have also admonished against judicial rewriting of claims to preserve validity . . . .

Rhine v. *Casio, Inc.*, 183 F.3d 1342, 1345 (Fed. Cir. 1999) (citations omitted). With this limitation in mind, the claim term being construed must first be reasonably capable of the interpretation that is purportedly favored by the arguments for invalidity. Thus, in employing this doctrine, the Court is not

permitted to construe a term that has a plain and ordinary meaning in a manner contrary to that meaning. This, of course, would constitute the type of "judicial rewriting" about which the Federal Circuit has warned. *See id.* Nor does it grant courts the authority to somehow jump to the conclusion that a claim term is reasonably susceptible of competing interpretations. Simply put, the doctrine does not grant courts the power to employ validity arguments to limit claim terms where such claim terms, even considering all alternative definitions, could not reasonably be construed to incorporate such limits. In such circumstances, validity concerns must lie in the province of the fact finder.

There is good reason, of course, to avoid conflating invalidity concerns with claim construction. First, the Court is mindful that determining whether a patent is invalid because it lacks a sufficient written description is an issue of fact. *See Union Oil Co. of Cal.* v. *Atl. Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000). As a result, in a jury case, the members of the jury should determine whether the patent adequately describes each element of the claimed invention. If the Court were to conflate invalidity concerns involving the written description requirement with claim construction, then a function reserved for the jury would be usurped by the trial judge. At the same time, the Supreme Court has made clear that construing the claims of a patent is an issue of law and, as such, claim construction is within the province of the trial judge. *See Markman*, 517 U.S. at 386. The conflict, then, becomes clear. If the Court were to select a construction that it believed was more consistent with the written description of the patent but contorted the language of the claim terms in order to do so, the jury, in effect, would be preempted from making the invalidity determination, which is within its province. This the Court cannot do.

Second, one must be cognizant that Congress has determined that "[a] patent shall be presumed valid." 35 U.S.C.

§ 282. This congressionally-mandated presumption of validity not only places the burden of proving invalidity on the defendant, but also requires the defendant to prove the point by clear and convincing evidence. *Sibia Neurosciences, Inc.* v. *Cadus Pharm. Corp.*, 225 F.3d 1349, 1355 (Fed. Cir. 2000). In order to give congressional will the deference it deserves, courts ought not permit defendants to shirk this responsibility by arguing that concerns regarding validity should be accounted for during claim construction. Instead, it strikes the Court that the proper way to proceed, where it is possible, is to interpret the claim terms consistent with their plain and ordinary meaning and hold the defendant to its burden to prove invalidity by clear and convincing evidence. Any other approach would neglect the congressional mandate.

In this case, the Court ruled during the *Markman* hearing that TKT's claim construction theory extends the canon that claims ought be construed in favor of their validity far beyond its intended reach. Instead, as explained below, because the terms to be construed simply are not reasonably capable of the interpretation proffered by TKT, it became apparent that TKT was actually attempting to add limitations to claim terms rather than merely attempting to define the disputed terms. At the end of the day, the canon that claims ought be construed so as to sustain their validity simply does not include under its umbrella TKT's arguments as they apply in this matter.

With these concerns in mind, the Court conducted the *Markman* hearing and interpreted ten words and phrases central to the patents-in-suit and the dispute between the parties. Each term, the arguments relevant to it, and the Court's construction are reproduced below seriatim.[10]

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[10] It should be noted that while the focus of the *Markman* hearing was on the patents themselves, the Court writes now with the benefit of having presided over the entire trial.

A. *Vertebrate Cells*

The term "vertebrate cells" is contained in Claims 4, 6, and dependent Claim 7 of the '698 patent and Claims 1, 4, and dependent Claims 3, 6, and 7 of the '349 patent. There is no contention by either party that the term should have a different meaning in the various claims. Aside from that agreement, however, the parties (not surprisingly) proffered quite different constructions. Amgen contended that "vertebrate cells" means "cells originating from an animal having a backbone," Pl.'s *Markman* Hr'g (Mar. 27, 2000) Demonstrative Ex. 12, whereas TKT argued that the term means "non-human cells that originate from an animal having a backbone," Defs.' *Markman* Hr'g Demonstrative Ex. 1. Thus, while Amgen proffered the broad, albeit ordinary meaning of the term, TKT sought to have the Court add a limitation to the claim by including the word "non-human."

The reason for the particular distinction between the parties' proffered constructions is, not surprisingly, fueled by the related infringement and validity analysis. In order to make EPO, TKT activates the native human EPO gene in a human cell. As a result, there is little wonder why TKT offered, and Amgen vehemently opposed, a construction of the term "vertebrate" that excluded human cells. Had the Court adopted TKT's version, it would have been bound to issue, upon proper motion, summary judgment of non-infringement—at least as to literal infringement. That, of course, is no reason to reject TKT's proffer, but merely explains the importance of construing the term appropriately.

While counsel for TKT admitted that its construction was contrary to the ordinary meaning of the term "vertebrate," TKT argued that "the terms of a claim cannot be construed in a vacuum." Tr. of *Markman* Hr'g, Vol. I at 7:17-18.[11] Instead,

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[11] Citations to transcripts refer to the page number followed by the line number of the referenced material.

implored TKT, the Court must interpret the claims in accordance with the specification and the prosecution history and, set in this context, "vertebrate cells" were not meant to encompass human cells even though humans are admittedly a subset of vertebrates. *Id.* at 7:22-25. For the reasons expressed above, however, TKT's contention is untenable. Even if significant intrinsic evidence pointed toward a more limited definition of "vertebrate," "the claim construction inquiry . . . begins and ends in all cases with the actual words of the claim. . . . [T]he resulting claim interpretation must, in the end, accord with the words chosen by the patentee to stake out the boundary of the claimed property." *Renishaw*, 158 F.3d at 1248 (citations omitted). There simply is no hook in the claim term that allows for TKT's alternate construction. The term "vertebrate" is a widely known and understood word which has a precise scientific meaning. A vertebrate is a member of the subphylum Vertebrata, which is a primary division of the phylum Chordata, which in turn is a division of the Animal Kingdom. A vertebrate is uniquely characterized by a segmented bony or cartilaginous spinal cord. Therefore, the plain and ordinary meaning of the term "vertebrate cells," i.e., cells that originate from an animal having a backbone, accords with the words chosen by the patentee to identify the scope of the claimed invention. Because humans are vertebrates, TKT's construction betrays the plain and ordinary meaning of the claim term. Thus, the Court construed the term "vertebrate cells" to mean "cells from an animal having a backbone." Tr. of *Markman* Hr'g, Vol. I at 67:8-9.

B. *Mammalian Cells*

The term "mammalian cells" is contained in Claim 1 of the '422 patent and dependent Claim 9 of the '698 patent. Consistent with its approach to vertebrate cells, TKT proffered a construction of the term "mammalian cells" that excluded human cells. Specifically, TKT contended that "mammalian

cells" are "[c]ells from warm-blooded non-human vertebrate animals whose young are fed by milk secreted from the mammary glands." Defs.' *Markman* Hr'g Demonstrative Ex. 1. Again, with an eye toward literal infringement, Amgen opposed this construction and instead argued that "mammalian cells" are "cells from a warm-blooded animal that has a backbone and whose young are fed by milk secreted from mammary glands." Pl.'s *Markman* Hr'g (Mar. 27, 2000) Demonstrative Ex. 14. For the same reasons explained above, the Court could not remain faithful to the widely known and specific meaning of the word "mammalian" if it were to add the non-human limitation. Simply put, the claim term was not reasonably susceptible to TKT's construction. As a result, the Court determined that "mammalian cells" are "cells from a warm-blooded animal, whose young are fed by milk secreted from mammary glands." Tr. of *Markman* Hr'g, Vol. I at 67:9-11.

C. *Mature Erythropoietin Amino Acid Sequence of Fig. 6*

This phrase is contained in Claims 4 and 6 of the '698 patent and Claims 2 and 3 of the '080 patent. Although the phrase sits in different contexts—and thus modifies different subjects—the parties agree that the phrase should have the same meaning in both settings. Focusing on the ordinary meaning of the term "mature," Amgen contended that the phrase means "the fully processed form of the protein secreted by a cell . . . when it transcribes and translates the DNA in Figure 6." *Id.* at 70:24 to 71:4. In contrast, relying on a portion of the specification that explains that "Fig. 6 thus serves to identify the primary structural conformation (amino acid sequence) of mature human EPO as including 166 specified amino acid residues," Trial Ex. 1 at 21:3-5,[12] TKT

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[12] Although the Court did not receive evidence during the *Markman* hearing, for the sake of unity throughout this decision, citations to the patent are made to what was eventually identified as Trial Exhibit 1.

contended that the phrase means "the 166 amino acid sequence of human EPO shown in Fig. 6,"[13] *see* Tr. of *Markman* Hr'g, Vol. I at 90:9 to 102:15. The dispute focused on the amino acid located in the 166th position, arginine. Unknown to Dr. Lin at the time of the invention, arginine is cleaved off at some point during protein synthesis prior to secretion from the cell. Thus, the protein that is actually secreted from the cell contains only 165 amino acids. Figure 6, however, depicts the arginine.

By proffering the language "fully processed," Amgen hoped to obtain an interpretation encompassing the secreted version of the protein, regardless of the specific number of amino acids. Meanwhile, TKT, whose process produces secreted proteins containing only 165 amino acids, sought an interpretation of Figure 6 that specifically required 166 amino acids.

The Court agreed that the term "mature" implied the fully processed form of EPO secreted by the cell, but whether "mature" included the 165 amino acid sequence as well as the 166 amino acid sequence was ambiguous. The patent specification used "mature" to describe an EPO polypeptide that has been secreted by a cell:

> the first residue designated for the amino acid sequence of the mature protein is indicative of the likelihood that EPO is initially expressed in the cytoplasm in a precursor form including a 27 amino acid "leader" region

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[13] TKT's early submissions to the Court regarding claim construction attempted to limit the DNA that encodes the mature erythropoietin amino acid sequence of Figure 6 to "cloned exogenous" human EPO DNA that encodes such sequence. Defs.' Claim Construction Submission (Sept. 20, 1999) at 19. Had TKT continued to press such a construction, the Court would have rejected it for the reasons previously explained. Simply put, no word or words in this disputed claim term are reasonably susceptible of this construction.

> which is excised prior to entry of mature EPO into circulation.

Trial Ex. 1 at 19:36-41. By identifying the EPO that enters circulation as "mature," Dr. Lin essentially defined the term "mature" to mean "the fully processed form of the protein that is secreted by the cell." Consequently, on the one hand, the Court agreed with Amgen's contention that "fully processed" or "fully realized" ought be incorporated into the Court's construction of the phrase "mature erythropoietin amino acid sequence of Fig. 6." On the other hand, the Court was not further persuaded by Amgen that reference to Figure 6 did not limit the meaning of the claim terms to the 166 amino acid sequence disclosed in that figure. Yet neither was TKT able to persuade the Court at the *Markman* hearing that the term was necessarily limited to a 166 amino acid construction. Consequently, the Court chose to abstain for the time being from deciding the "165-166 dispute" and concluded only that the phrase "the mature erythropoietin amino acid sequence of Figure 6" means "the fully realized form of amino acid sequence of Figure 6." Tr. of *Markman* Hr'g, Vol. II at 23:14-18.

D. *Non-human DNA Sequences That Control Transcription and Transcription Control DNA Sequences*

As background, transcription is the process whereby RNA polymerase copies genetic information contained in a DNA nucleotide sequence into a complementary RNA sequence. As the patent explains, "the programming function of DNA is generally effected through a process wherein specific DNA nucleotide sequences (genes) are 'transcribed' into relatively unstable messenger RNA (mRNA) polymers." Trial Ex. 1 at 1:52-55. Transcription is a critical step in the expression of proteins like erythropoietin and is itself controlled by its own DNA sequences. These "transcription control DNA sequences" "precede a selected gene (or series of genes) in a functional DNA polymer [and] cooperate to determine

whether the transcription (and eventual expression) of a gene will occur." *Id.* at 2:10-13. According to the patent, "transcription control sequences" is the collective term for DNA sequences that not only "provide a site for initiation of transcription into mRNA," but also are capable of binding proteins that determine "the frequency (or rate) of transcriptional initiation." *Id.* at 2:3-12. Claims referring to these transcription control sequences were the subject of the following disputes between the parties.

The phrase "non-human DNA sequences that control transcription" is contained in Claim 1 of the '349 patent. Amgen contended that this phrase means "[n]on-human DNA sequences that are able to initiate or regulate RNA synthesis from EPO DNA." Pl.'s *Markman* Hr'g (Mar. 27, 2000) Demonstrative Ex. 69. In contrast, TKT argued that the phrase means "DNA sequences which did not originate in the human genome, which initiate and regulate RNA synthesis of adjacent DNA, and which replace the human EPO transcription control sequences." Defs.' *Markman* Hr'g (Mar. 27-28, 2000) Demonstrative Ex. 1. The dispute centered around a few crucial terms.

First, TKT contended that in order to "control" transcription, the DNA sequences must both initiate *and* regulate the transcription of a gene. Amgen objected to the use of "and," preferring a construction that required DNA sequences either to initiate *or* regulate transcription.

Second, the parties disputed the importance of location. By including the term "adjacent DNA" in its construction, TKT sought to require the DNA sequences that control transcription to be located in a position adjacent to the gene segment intended to be expressed.

Third, the parties disagreed as to the meaning of "non-human." Amgen argued that "non-human" means "not part of the human genome," whereas TKT contended that it means

"not originating in the human genome." Because it is scientifically arguable that viral DNA originates in the human genome, the viral promoter DNA that TKT employs thus might not fall within the meaning of the claim.

The Court first determined that "non-human" DNA sequences are DNA sequences that are "not part of the human genome." Tr. of *Markman* Hr'g, Vol. II at 55:25 to 57:1. The Court rejected TKT's construction, ruling that Amgen meant simply to exclude the human DNA sequences that control transcription from the reach of its claim, sequences which, of course, are part of the human genome. By construing the term "non-human" to mean "not part of the human genome," then, the Court settled on a construction that best effectuated Amgen's intent.

Second, the Court rejected TKT's "adjacent" language because no claim term could reasonably be construed to be limiting the transcription control DNA sequences by their location. Consequently, the Court adopted a construction that was in no way limited by the location of the transcription control sequences relative to the gene to be expressed.

Third, the Court held that "DNA sequences that control transcription are DNA sequences that initiate and may regulate the processes of transcription." *Id.* at 57:1-4. When it announced its construction of this phrase, the Court used the term "may," which signifies that while the DNA sequence must initiate transcription, it need not regulate transcription.

The Court then considered the phrase "transcription control DNA sequences," which is contained in Claim 4 of the '349 patent. Borrowing extensively from the patent specification, the Court explained that "transcription control sequences" are "collectively promoter DNA sequences that provide a site that is capable of initiating transcription . . . and regulator DNA sequences that are capable of binding proteins that determine the frequency or rate . . . of transcription initiation." *Id.* at

57:16-23. At the time, the Court did not recognize the inconsistency between these two constructions. Although "DNA sequences that control transcription" and "transcription control DNA sequences" should have the same meaning, the Court's constructions permitted regulator functions in one instance and required them in the other instance. As will be explained in the infringement portion of the decision, however, the parties tried the case with the latter construction in mind and thus no harm to the parties resulted.

E. *Purified from Mammalian Cells Grown in Culture*

The phrase "purified from mammalian cells grown in culture" is contained only in Claim 1 of the '422 patent, for which the Court subsequently granted summary judgment on literal infringement grounds. The parties presented strikingly different constructions of this phrase during the *Markman* hearing. Amgen contended it means "[p]urified from the in vitro culture in which the mammalian cells have been grown," Pl.'s *Markman* Hr'g (Apr. 10, 2000) Demonstrative Ex. Amgen's '422 Patent Claim 1, whereas TKT argued that it means "obtained in a substantially homogeneous state from the mammalian cells in which it was produced and not from the cell culture media," Defs.' *Markman* Hr'g (Apr. 10, 2000) Demonstrative Ex. 50. TKT admitted that the specification taught three different methods of obtaining EPO: extraction (1) from the cell cytoplasm; (2) from the cell membrane; and (3) from the cell culture medium. TKT nonetheless contended that the plain and ordinary meaning of the phrase meant that the EPO had to be purified from the cells. Thus, argued TKT, Amgen only claimed one of the three methods it taught in the patent. Because TKT obtains its EPO from the cell culture media and not directly from its cells, the parties' positions are not surprising.

The Court, however, disagreed with TKT's interpretation of the claim with respect to both the plain and ordinary meaning of the terms and the consistency of its interpretation

with the other claims. First, TKT's construction would exclude the patent's preferred embodiment: Example 10. Constructions that exclude the patent's preferred embodiment should rarely be adopted. *Modine Mfg. Co.* v. *United States Int'l Trade Comm'n*, 75 F.3d 1545, 1550 (Fed. Cir. 1996); *MediaCom*, 4 F. Supp. 2d at 28. Example 10 extensively describes techniques for obtaining substantially purified erythropoietin from cell culture media. Trial Ex. 1 at 27:15-50, 28:29-32. TKT's claim construction would exclude the method taught in the patent's preferred embodiment and hence is suspect.

Second, from the Court's perspective, TKT's construction ignored the language "grown in culture" and focused solely on the immediately preceding language, "purified from mammalian cells." If the claim merely read "purified from mammalian cells," then TKT's argument that the human erythropoietin must be extracted from the cell itself would indeed have held more sway. Yet all of the terms of the claim must be given effect. Consequently, the Court read the phrase "mammalian cells grown in culture" as a whole and, therefore, as not specifying a particular method, but rather encompassing purification techniques from the cells or the cell culture medium. Thus, the Court held that "purified from mammalian cells grown in culture" means "obtained in substantially homogeneous form from the mammalian cells, using the word from in the sense that it originates in the mammalian cells, without limitation to it only taking it directly out of the interior of the cells, which have been grown in the in vitro culture." Tr. of *Markman* Hr'g, Vol. III at 16:15-19.

F. *DNA Encoding Human Erythropoietin*

The phrase "DNA encoding human erythropoietin" is contained in Claim 1 and related to dependent Claims 3 and 7 of the '349 patent. Amgen, on the one hand, contended that the claim terms are so straightforward that interpretation of

any of the terms was unnecessary. TKT, on the other hand, argued that the phrase means "[h]uman EPO DNA that is exogenous to the cell in which the EPO is produced, i.e., the human EPO DNA did not originate in the genome of the cell into which it is inserted," Defs.' *Markman* Hr'g (Apr. 10, 2000) Demonstrative Ex. 19—more succinctly, "exogenous DNA encoding human erythropoietin." TKT argued that because the patent specification only taught using DNA that encoded for human erythropoietin that did not originate in the genome of the host cell (exogenous DNA), the claim term should not be interpreted to include both exogenous and endogenous human EPO DNA. Because TKT activates the human erythropoietin gene in the human host cell (the endogenous EPO gene), one can understand TKT's motivation in proffering its construction.

Yet, as the Court pointed out, TKT's construction is merely "a variant of the argument that's already been made here." Tr. of *Markman* Hr'g, Vol. III at 23:2-3. TKT was once again employing invalidity contentions in an attempt to add limitations into claim terms that by their plain meaning were not amenable to such limitations. The plain meaning of the claim terms simply do not call for any such limitation. This portion of the claim language claims any and all DNAs that encode human erythropoietin regardless of such DNA's relationship to the host cell in which it is expressed. Thus, the Court held that "DNA encoding human erythropoietin" means "DNA which encodes human erythropoietin, not including the word exogenous DNA which encodes human erythropoietin." *Id.* at 35:1-3.[14]

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[14] While such a construction, in light of its tautology, probably would neither satisfy a third grade English teacher nor be a sufficient dictionary definition, it was nonetheless more than sufficient to aid the parties and the Court in organizing the presentation of evidence.

G. *Operatively Linked*

"Operatively linked" is located in Claim 4 of the '698 patent and related by dependency to Claims 5 and 9. In context, the phrase relates to the relationship between promoter DNA[15] and the DNA that is transcribed downstream from the promoter DNA. Amgen contended that the phrase means "[p]ositioned such that it provides for initiation of transcription of a gene." Pl.'s *Markman* Hr'g (Apr. 10, 2000) Demontrative Ex. Amgen's '698 Patent Claim 4. TKT argued that the term means "[positioned adjacent] to the DNA encoding EPO in a way that maintains the capability to initiate transcription of EPO DNA." Defs.' *Markman* Hr'g (Apr 10, 2000) Demonstrative Ex. 69 (alteration in original). The parties disputed, once again, the issue of the location of the promoter relative to the gene to be expressed. Amgen argued that the words "operatively linked" imposed no locational restriction, whereas TKT contended that because the patent taught placing the promoter DNA immediately adjacent to the DNA encoding EPO, the term "operatively linked" ought be limited by location.

The term "linked" could, if unmodified by "operatively," imply a spatial relationship in that a link could fix the maximum distance between the two linked objects. Yet modification by the term "operatively" implies a functional rather than physical link between the two objects—in this instance one entity's exertion of influence on another entity. More specifically, in this case, the link between the promoter DNA and DNA encoding EPO consists of the influence possessed by the promoter DNA to initiate the transcription from the DNA encoding EPO. As a result, the term

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[15] Promoter DNA is a segment of DNA that serves to determine where RNA polymerase begins synthesis of RNA from DNA. Here, promoter DNA refers to the DNA segment that determines where RNA polymerase begins the synthesis of RNA that transcribes from the DNA encoding EPO.

"operatively linked" is not defined by the physical location of the promoter DNA relative to the DNA encoding erythropoietin, but rather by the functional effect the promoter DNA has on the EPO DNA. Thus, contrary to TKT's contentions, the term "operatively linked" could not reasonably be construed to impose a locational restriction, because the link is limited only in the sense that the promoter DNA must initiate transcription of the EPO DNA. Consequently, the Court determined that "operatively linked" means "the promoter DNA is linked to the EPO DNA in a way that maintains the capability of the promoter DNA to initiate transcription of the EPO DNA." Tr. of *Markman* Hr'g, Vol. III at 43:8-10.

H. *Non-naturally Occurring*

The phrase "non-naturally occurring" modifies the erythropoietin glycoprotein product claimed in the '933 patent, Claims 1 and 2 and dependent Claim 9, as well as Claim 3 and dependent Claim 4 of the '080 patent. TKT argued that the phrase was meant to incorporate the exogenous DNA limitation that it had sought (unconvincingly) with respect to many of the prior construed claim terms. Thus, it proffered the following definition: "produced from an EPO DNA coding sequence which was not part of the native genome of the host cell in which the EPO protein is produced. . . ." Defs.' *Markman* Hr'g Demonstrative Ex. 36. Amgen, in contrast, contended that the term means "[o]btained from a source that does not naturally produce or contain EPO." Pl.'s *Markman* Hr'g (Apr. 10, 2000) Demonstrative Ex. Amgen's '933 Patent Claim 1 (emphasis omitted). The contentions conflicted in this manner because TKT activates an endogenous EPO gene in a human cell, as opposed to generating EPO from an exogenous gene transfected into a host cell.

Unlike the prior instances in which TKT attempted to impose the exogenous DNA limitation into the construction of a claim term, there is a reasonable argument that the term

"non-naturally occurring" has the meaning that TKT attempted to ascribe to it because, to put it simply, there *is* something a bit "non-natural" about an erythropoietin glycoprotein being produced by transfecting host cells with exogenous EPO DNA. Yet TKT's interpretation is deficient for various reasons.

First, TKT's ship runs aground on the claim construction axiom that a claim will not be construed as containing a limitation that is expressed in other claims. *See Karlin Tech. Inc.* v. *Surgical Dynamics, Inc.*, 177 F.3d 968, 971-72 (Fed. Cir. 1999). Similarly, "[a]ll the limitations of a claim must be considered meaningful," *Unique Concepts, Inc.* v. *Brown*, 939 F.2d 1558, 1562 (Fed. Cir. 1991) (citation omitted), and if two separate and distinct limitations are construed as synonymous, the claim recitation of both limitations is redundant and superfluous. *See Beachcombers, Int'l* v. *Wildewood Creative Prods. Inc.*, 31 F.3d 1154, 1162 (Fed. Cir. 1994); *Tex. Instruments, Inc.* v. *United States Int'l Trade Comm'n*, 988 F.2d 1165, 1171 (Fed. Cir. 1993). Claim 3 of the '933 patent, though not in suit, claims a "non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin . . . ." If the Court were to adopt TKT's construction of "non-naturally occurring," it would render the terms redundant in the context of the '933 patent's Claim 3. Thus, neither the patentee nor the examiner could have meant the term "non-naturally occurring" to refer to the use of exogenous EPO DNA.

Second, the patent specification also explains that the recombinant-produced and synthetic products are both similar to and different from natural EPO. For example, one passage compares the biological activity of the synthetic products to that of "EPO isolates from natural sources" or "natural EPO isolates." Trial Ex. 1 at 33:14, 33:24; *see id.* at 33:40-44. Thus, the specification indicates that Dr. Lin contemplated his

polypeptide products vis-a-vis the unpatentable EPO polypeptide from natural sources. Furthermore, the Supreme Court has used the term "nonnaturally occurring" to distinguish a "product of human ingenuity" from the "natural phenomenon" that the non-natural version mimics. *See Diamond* v. *Chakrabarty*, 447 U.S. 303, 309-10 (1980). In considering the terms "non-naturally occurring" here, the Court held that Dr. Lin intended a similar meaning. By including this limitation, Dr. Lin meant to stand clear of the unpatentable, naturally occurring products. He intended nothing more.

In light of these considerations, after taking the matter under advisement on April 10, 2000, the Court informed the parties at the final pretrial conference on April 18, 2000 that "non-naturally occurring" means "not occurring in nature."

I. *Glycosylation Which Differs*

The phrase "glycosylation which differs" is recited only in Claim 1 of the '933 patent and relates to Claims 2 and 9 of the same patent by dependency. The parties essentially agreed that glycosylation refers to the carbohydrate side chains that are attached to a molecule, in this case erythropoietin. Yet Amgen further contended that the phrase means that "[t]he attached carbohydrate groups differ when analyzed by standard prior art techniques known as of 1983-84." Pl.'s *Markman* Hr'g (Apr. 10, 2000) Demonstrative Ex. Amgen's '933 Patent Claim (emphasis omitted). TKT argued that it means "the carbohydrate groups attached to side chains of the erythropoietin polypeptide backbone differ by Western blot analysis and SDS/PAGE[16] and carbohydrate composition

[16] Sodium dodecylsulfate-polyacrylamide gel electrophoresis ("SDS-PAGE") is a widely used procedure for determining the apparent molecular weight of a particular protein or glycoprotein. The Western Blot is a technique for detecting the particular protein or glycoprotein following SDS-PAGE. SDS-PAGE techniques and their relation to glycosylation differences are discussed later. *See infra* Section IV.E.2, at 130-32.

analysis[17] from those of human urinary erythropoietin to at least the degree described in the patents-in-suit. Defs.' *Markman* Hr'g (Apr. 10, 2000) Demonstrative Ex. 89 (footnotes added). The primary discrepancy concerned which, if any, techniques would be specifically identified as methods encompassed under the meaning of the term "glycosylation which differs." TKT contended that the specification describes two tests by which to prove differences in glycolsylation: SDS-PAGE/Western Blot and carbohydrate composition analysis. Thus, TKT's construction would require proof with respect to both types of tests and no others, whereas Amgen's construction would not limit the manner by which differences in glycosylation are proven.

Example 10 of the patent describes comparisons made between recombinant glycoprotein products and human urinary erythropoietin using various techniques. *See* Trial Ex. 1 at 28:33-67. The specification not only reports data obtained from SDS-PAGE/Western blot analysis, but also by monosaccharide, or carbohydrate, analysis. *See id.* Yet the claim term "glycosylation which differs" is not further limited by the methods used to identify such differences in Example 10. A comparison of Claims 1 and 2 of the '933 patent exposes the significance of the exclusion of such a limitation. Claim 2 of the '933 patent requires the EPO glycoprotein product to have "a higher molecular weight than human urinary EPO *as measured by SDS-PAGE*." *Id.* at 38:23-25 (emphasis added). Claim 1, however, merely states that the erythropoietin glycoprotein product must have "glycosylation which differs from that of human urinary erythropoietin." *Id.* at 38:20-21. The inference is that the patentee knew how to limit claim terms regarding differences in glycosylation by specifying the method by which such differences are

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[17] Carbohydrate analysis reveals the ratio of specific sugars present in a glycoprotein. It is discussed in more detail later. *See infra* Section IV.E.2, at 134-36.

empirically tested. Taking this into account, the Court was loath to mandate that proof of glycosylation differences must be shown using the particular types of tests specifically identified in the patent. As a result, the Court avoided mandatory language, but nonetheless ruled that "glycosylation which differs" means: "Glycosylation as to which there is a detectable difference based upon what was known in 1983-1984 from that of human urinary erythropoietin, having in mind that the patent holder, Amgen, taught the use of this Western blot, SDS-PAGE and monosaccharide test." Tr. of *Markman* Hr'g, Vol. III at 102:1823.

J. *Human Urinary Erythropoietin*

The '933 patent employs the phrase "human urinary erythropoietin" in Claims 1 and 2 and dependent Claim 9. Trial Ex. 2 at 38:21, 38:23, 39:3. Amgen contended that the term means "[h]uman EPO isolated from pooled urine of aplastic anemia patients isolated using any method used in the prior art," Pl.'s *Markman* Hr'g (Apr. 10, 2000) Demonstrative Ex. Amgen's '933 Patent: The Parties Constructions (emphasis omitted), whereas TKT argued that it means "[a]ll EPO preparations that can be isolated or purified from human urine by any method," Defs.' *Markman* Hr'g (Apr. 10, 2000) Demonstrative Ex. 2. The dispute, then, is essentially one of scope: Does the claim term encompass all erythropoietin preparations obtained from human urine or is it limited to only EPO obtained from the pooled urine of aplastic anemia patients?

In order to support its construction, Amgen relied on the specification and prosecution history. The specification, for instance, identifies and briefly describes the "Miyake procedure"[18] for "purifying human erythropoietin from urine of patients with aplastic anemia." Trial Ex. 1 at 7:10-17. The

[18] The Miyake procedure is a particular method for purifying urinary EPO.

patent cites other prior art sources that describe the isolation of human urinary erythropoietin from the pooled urine of aplastic anemia patients. *Id.* at 8:13-16. The specification also reports the results relating to molecular weight comparisons of CHO-produced EPO, COS-produced EPO, and the "pooled source human urinary extract."[19] *Id.* at 28:33-41. Similarly, Amgen pointed to comparisons between its recombinant erythropoietin and human urinary erythropoietin purified by the Miyake procedure as evidence of novelty. Trial Ex. 2 Tab 6 at 11.

Though Amgen's construction may be supported by these aspects of the specification and prosecution history, Amgen's narrow interpretation of this claim limitation is not faithful to the plain and ordinary meaning of the claim language. The claim terms themselves do not specify which type of human urinary erythropoietin is contemplated. Instead, the plain and ordinary meaning of the phrase "human urinary erythropoietin" broadly encompasses all urinary EPOS. As a result, "on this one, in all candor, the shoe is on the other foot . . . ." Tr. of *Markman* Hr'g, Vol. III at 106:11-12. Thus, adhering to the plain meaning of the terms, the Court concluded that "human urinary erythropoietin" means "erythropoietin derived from human urine." *Id.* at 112:23-24.

III. SUMMARY JUDGMENT OF INFRINGEMENT ON CLAIM 1 OF THE '422 PATENT

Following the *Markman* hearing, the Court turned promptly—albeit in an entirely separate hearing, *see supra* Part II—to considering the then pending motion for summary judgment. On April 26, 2000, the Court heard oral argument regarding whether TKT's activities literally infringe Claim 1 of the '422 patent and Claims 1, 3, 4, and 6 of the '349 patent. Amgen argued that there were no genuine issues of material

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[19] CHO, or Chinese hamster ovary, cells are, as their name suggests, derived from hamsters. COS cells are, in contrast, derived from monkeys.

fact regarding the technologies of each party and that a plain reading of the claims of Amgen's patents entitled Amgen to judgment as matter of law.

Summary judgment is appropriate when there are no genuine issues of material fact and the movant is entitled to judgment as matter of law. Fed. R. Civ. P. 56. Nonetheless, the Court must view the evidence in the light most favorable to the non-movant and must draw all reasonable inferences and resolve all doubts regarding factual issues in favor of the party opposing summary judgment. *Pfaff* v. *Wells Elecs., Inc.*, 5 F.3d 514, 517 (Fed. Cir. 1993). In considering a motion for summary judgment, the Court relies upon any "'pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits'" which, in toto, comprise the relevant record. *Rotec Indus., Inc.* v. *Mitsubishi Corp.*, 215 F.3d 1246, 1250 (Fed. Cir. 2000) (quoting Fed. R. Civ. P. 56[c]). As is required under controlling law, the Court considers only the documents in the summary judgment record as of April 26, 2000.

As this Court has previously held, "if there are no genuine issues of material fact, summary judgment is appropriate in a patent infringement case as in any other." *Amgen, Inc.* v. *Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 107 (D. Mass. 1998). Infringement is a two-part inquiry requiring the construction of the claims, which is a question of law, and the application of the properly construed claims to the allegedly infringing article, which is a question of fact. *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370, 391 (1996); *Renishaw Plc* v. *Marposs Societa' Per Azioni*, 158 F.3d 1243, 1247-48 (Fed. Cir. 1998).

When the parties do not dispute relevant facts regarding infringement, but merely disagree over claim construction, "the question of literal infringement collapses to one of claim construction and is thus amenable to summary judgment." *Athletic Alternatives, Inc.* v. *Prince Mfg., Inc.*, 73 F.3d 1573,

1578 (Fed. Cir. 1996); *see K-2 Corp.* v. *Salomon S.A.*, 52 U.S.P.Q.2d (BNA) 1001, 1004 (Fed. Cir. 1999). In contrast, when the Court construes the claims in favor of the plaintiff, and a genuine issue of material fact regarding infringement nonetheless exists, summary judgment is not appropriate. *See MacNeill Eng'g Co.* v. *Trisport, Ltd.*, No. 98-12019, slip op. at 17 n.3 (D. Mass. Jan. 10, 2001). With these considerations in mind, the Court addressed the legal issue whether, upon the summary judgment record, TKT's product, HMR 4396, and TKT's R223 cells literally infringe Claim 1 of the '422 patent.

Claim 1 of the '422 patent claims a "pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture." Trial Ex. 6 at 38:36-40. As Federal Circuit precedent requires, the Court broke down Claim 1 into each of its limiting terms and compared those terms—and any meanings ascribed to them during the *Markman* hearing—with TKT's HMR4396 and R223 cells.

A. *Pharmaceutical Composition*

Amgen submitted ample and uncontradicted evidence on the summary judgment record that TKT's HMR4396 injection is a pharmaceutical composition. As explained in Section 3.6 of TKT's Investigational New Drug Application ("IND") for HMR4396, which is submitted to the Food and Drug Administration ("FDA") in order to initiate and facilitate the agency's clinical investigation of the product, "HMR4396 Injection is a sterile, nonpyrogenic, colorless aqueous solution in Water for Injection at 4000 U/ml or 10,000 U/ml concentrations." Galvin Decl. (Nov. 4, 1999) Ex. 10 at IND000019. Furthermore, the fact that the product has been submitted for investigation by the FDA is clear evidence that HMR4396 is a pharmaceutical composition. Another IND

document describes diluting the HMR4396 purified bulk "to obtain the desired drug product dosage strengths . . . ." *Id.* Ex. 18 at IND501303; *see id.* Ex. 1 at 242:9 to 243:25, 282:8-21 (explaining that HMR4396 is an aqueous solution that is further formulated into a pharmaceutical composition). In light of this uncontradicted evidence, HMR4396 is a pharmaceutical composition as that term is used in Claim 1 of the '422 patent.

B. *Therapeutically Effective Amount of Human Erythropoietin*

It cannot be disputed that HMR4396 is human erythropoietin. Section 3.3 of the IND for TKT's "Gene-Activated Erythropoietin" directly states that "HMR4396 is human erythropoietin produced by TKT's gene-activation technology." *Id.* Ex. 10 at IND000019; *see id.* Ex. 14 at IND000335-37, 000385 (identifying HMR4396 as human erythropoietin). Furthermore, in response to the question whether HMR4396 is human erythropoietin, TKT's Federal Rule of Civil Procedure 30(b)(6) designee, David S. Johnson, answered affirmatively. *Id.* Ex. 4 at 37:10-11. Another TKT Rule 30(b)(6) designee, Richard F. Selden, admitted that HMR4396 is human erythropoietin. Stretch Decl. (Apr. 20, 2000) Ex. 4 at 399:1519; *see* Galvin Decl. (Nov. 4, 1999) Ex. 1 at 14:12 to 15:6.

In the face of these significant admissions, TKT opted to take two tacks, but neither steadied its rocking boat because both were unsuccessful attempts at changing the Court's claim construction rather than efforts to raise an issue of disputed material fact. First, in its initial response to Amgen's summary judgment motion and during subsequent argument, TKT contended that HMR4396 was not human erythropoietin because as that term is used in the patent "human erythropoietin" means recombinant EPO produced in non-human cells transfected with cloned, exogenous human EPO DNA. Because HMR4396 is produced by activating the endogenous

EPO gene in a human cell, such a construction would exclude TKT's product. This contorted claim construction, however, was rejected by the Court. *See supra* Section II.F, at 33-34.

Second, during oral argument following claim construction, TKT attempted to add a further limitation into the claim. Relying on language from the specification regarding Claim 1 of the '422 patent that explained that the pharmaceutical composition was comprised of "effective amounts of polypeptide products of the invention," Trial Ex. 6 at 12:6-7, TKT argued that "human erythropoietin" should be limited by this phrase. Thus, contended TKT, because the polypeptide products of the invention are defined in part by Figure 6, *see id.* 11:42-54, which erroneously specifies a 166 amino acid chain, *see* Trial Ex. 1 Fig. 6, and TKT only isolates a 165 amino acid product, HMR4396 could not be human erythropoietin. TKT thus seeks to read a 166 amino acid limitation into the claim term "human erythropoietin." This the Court cannot do. As with the previous tack, this argument drifted far astray from the language of the claim and was therefore unpersuasive. Rather than attack the Court's claim construction, to forestall summary judgment, TKT needed to point to *evidence* that would demonstrate a genuine issue of material fact regarding infringement *in the context of* the Court's construction. Because it failed to do so, and Amgen's evidence on the same point was substantial, the Court determined that HMR4396 is human erythropoietin.

Moreover, when asked by the Court whether HMR4396 contains a therapeutically effective amount of human erythropoietin, counsel for TKT admitted that, "If it didn't, believe me, we wouldn't be standing here." Tr. of *Markman* Hr'g, Vol. II at 130:19-20. As admissions on the record constitute evidence upon which reliance may be placed at the summary judgment stage, *see* Fed. R. Civ. P. 56(c), counsel's direct answer is more than sufficient to warrant summary judgment of infringement with respect to this claim term.

Counsel's response also comports with the common sense context of this case. TKT's product would simply pose no real threat to EPOGEN® if it did not contain a therapeutically effective amount of human erythropoietin. Patients would not seek, nor doctors prescribe, such an ineffective product. Viewed in this context, TKT's admission made perfect sense. As a result, the Court determined on the summary judgment record that HMR4396 contained a therapeutically effective amount of human erythropoietin.

C. *Pharmaceutically Acceptable Diluent, Adjuvant, or Carrier*

The evidence on the summary judgment record with respect to HMR4396 showed that it contains a phosphate buffer that acts as a diluent. In particular, as TKT's Rule 30(b)(6) designee explained, once the bulk is generated from the culturing of the human cells, the product is then diluted to provide a product of desired strength. Galvin Decl. (Nov. 4, 1999) Ex. 1 at 243:1219. The diluent is a phosphate buffer that "affords the pH control in the formulation." *Id.* at 243:5-6. The uncontroverted admissions in the Hancock deposition testimony satisfactorily proved that HMR4396 contains a pharmaceutically acceptable diluent, adjuvant, or carrier.

D. *Purified from Mammalian Cells Grown in Culture*

Claim 1 of the '422 patent claims a pharmaceutical composition comprising human erythropoietin that has been purified from mammalian cells grown in culture. Trial Ex. 6 at 38:40-41. In light of the Court's constructions of "mammalian cells" and "purified from mammalian cells grown in culture," *see supra* Section II.B, at 23-24, Section II.E, at 31-33, the Court considers the evidentiary record. The record makes clear that TKT's R223 cell line, which is used to make HMR4396, is derived from an HT1080 cell, which is a human skin cancer cell. Thus, although the cell undergoes a variety of changes during TKT's process, it is—and at all times

remains—a human cell. *See* Galvin Decl. (Nov. 4, 1999) Ex. 4 at 74:14 to 75:12. TKT's approach to this claim term depended entirely on persuading the Court that "mammalian" did not include "human." As explained above, the Court rejected this proffered construction, leaving TKT in the Herculean position of proving that humans were somehow not mammalian. Not surprisingly, they opted instead to concede on the summary judgment record that the R223 cells are mammalian cells under the Court's construction. Tr. of *Markman* Hr'g, Vol. II at 130:21-25. Consequently, the Court determined that TKT employs mammalian cells. *Id.* at 136:1-2.

With respect to the purification process, the evidence on the summary judgment record shows that TKT purifies its EPO from the cell culture supernatant or media rather than directly from the interior of the cells. Stretch Decl. (Apr. 20, 2000) Ex. 3 at 20:18-25. Having failed to convince the Court to adopt its limiting construction of "purified in mammalian cells grown in culture", TKT saw the writing on the wall and, rather than attempt to adduce evidence indicating that TKT did not literally infringe the claim term as it had been construed by the Court, elected to request that the Court reconsider its construction. The Court declined to do so, and as a result, and in reliance on additional summary judgment evidence, it determined that TKT's purification process literally infringed the relevant claim language. *See* Galvin Decl. (Nov. 4, 1999) Ex. 1 at 311:19-25 to 312:2-8; *id.* Ex. 5 at 693:1-16.

E. *Conclusion*

Because HMR4396 is a pharmaceutical composition comprising a diluent and a therapeutically effective amount of human erythropoietin which is purified from mammalian cells grown in culture, the Court ruled on the summary judgment record that HMR4396 infringed Claim 1 of the '422 patent. To this extent, the Court granted Amgen's summary

judgment motion [docket no. 211]. As to all remaining claims under consideration, the Court denied summary judgment.

IV. FINDINGS OF FACT

A. *Parties, Patents, and Products*

Amgen is a Delaware corporation with its principal place of business in Thousand Oaks, California. Joint Pretrial Mem. at 3, ¶ 1. Hoechst Marion Roussel, Inc.—now known as Aventis Pharmaceuticals, Inc.—is a Delaware corporation with its principal place of business in Bridgewater, New Jersey. *Id.* at 3, ¶ 2. TKT is a Delaware corporation with its principal place of business in Cambridge, Massachusetts. *Id.* at 3, ¶ 3. The Court has subject matter jurisdiction over the claims asserted in Amgen's Amended Complaint pursuant to 28 U.S.C. §§ 1338(a) and 2201-02. Venue is proper in accordance with 28 U.S.C. §§ 1391 and 1400 (b).

The five patents-in-suit include the '933 patent, the '698 patent, the '080 patent, the '349 patent, and the '422 patent. *Id.* at 3-4, ¶¶ 5-9. Amgen seeks to enforce the following claims of each patent:

The '933 patent:

> 1. A non-naturally occurring erythropoietin glycoprotein product having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and having glycosylation which differs from that of human urinary erythropoietin.
>
> 2. The non-naturally occurring EPO glycoprotein product according to claim 1 wherein said product has a higher molecular weight than human urinary EPO as measured by SDS-PAGE.

9. A pharmaceutical composition comprising an effective amount a glycoprotein product effective for erythropoietin therapy according to claim 1, 2, 3, 4, 5, or 6 and a pharmaceutically acceptable diluent, adjuvant or carrier.

. . . .

Trial Ex. 2 at 38:17-25, 39:1-4.

The '698 patent:

4. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:

a) growing, under suitable nutrient conditions, vertebrate cells comprising promoter DNA, other than human erythropoietin promoter DNA, operatively linked to DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and

b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.

5. The process of claim 4 wherein said promoter DNA is viral promoter DNA.

6. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:

a) growing, under suitable nutrient conditions, vertebrate cells comprising amplified DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and

b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.

7. The process of claim 6 wherein said vertebrate cells further comprise amplified marker gene DNA.

8. The process of claim 7 wherein said amplified marker gene DNA is Dihydrofolate reductase (DHFR) gene DNA.

9. The process according to claims 2, 4 and 6 wherein said cells are mammalian cells.

Trial Ex. 4 at 38:39-64.

The '080 patent:

2. An isolated erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6 and is not isolated from human urine.

3. A non-naturally occurring erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6.

4. A pharmaceutical composition comprising a therapeutically effective amount an erythropoietin glycoprotein product according to claim 1, 2, or 3.

. . . .

Trial Ex. 3 at 38:39-53.

The '349 patent:

1. Vertebrate cells which can be propagated in vitro and which are capable upon growth in culture of pro-

ducing erythropoietin in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay, said cells comprising non-human DNA sequences that control transcription of DNA encoding human erythropoietin.

. . . .

3. Vertebrate cells according to claim 1 capable of producing in excess of 1000 U erythropoietin per 10^6 cells in 48 hours.

4. Vertebrate cells which can be propagated in vitro which comprise transcription control DNA sequences, other than human erythropoietin transcription control sequences, for production of human erythropoietin, and which upon growth in culture are capable of producing in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay.

. . . .

6. Vertebrate cells according to claim 4 capable of producing in excess of 1000 U erythropoietin per 10^6 cells in 48 hours.

7.A process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, vertebrate cells according to claim 1, 2, 3, 4, 5, or 6.

Trial Ex. 5 at 38:8-14, 38:18-27, 38:31-36.

The '422 patent:

1. A pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture.

Trial Ex. 6 at 38:36-40.

In conjunction with his research team, Amgen scientist Dr. Fu-Kuen Lin was the inventor of the inventions claimed in this group of patents. *See* Trial Tr. at 957:21 to 958:18. Amgen owns all five patents by assignment. Trial Exs. 140-49. All five patents share a common disclosure and specification while the claims, of course, vary. *See* Joint Pretrial Mem. at 4, ¶ 10.

Amgen manufactures and sells a human erythropoietin pharmaceutical product known as epoietin alfa under the trademark EPOGEN®. Trial Tr. at 957:8-11. Specifically, EPOGEN® is the product of Example 10 of the patents-in-suit. *See id.* at 957:818, 1044:9-20.

In collaboration with TKT, Hoechst is developing HMR4396. *See* Joint Pretrial Mem. at 4, ¶ 12. HMR4396 is human erythropoietin. *See supra* Section III.B, at 48-50. HMR4396 is produced from the R223 cell line grown in culture. Joint Pretrial Mem. at 4, ¶ 13. Lonza Biologics, Inc. manufactures HMR4396 in the United States under a contract between TKT and Lonza Biologics PLC (the parent company of Lonza Biologics, Inc.). *Id.* at 4, ¶ 14. Using HMR4396 produced in the United States, Gruppo Lepetit, S.p.A. in Anagni, Italy currently formulates HMR4396 Injection. *Id.* at 4, ¶ 16. Ben Venue Laboratories, Inc. previously formulated HMR4396 Injection in the United States pursuant to a contract between TKT and Ben Venue. *Id.* at 4, ¶ 15. TKT intends to file a Biologics License Application for HMR4396 with the FDA. *Id.* at 4, ¶ 17. In addition, it is seeking regulatory approval to make and sell HMR4396 produced from the R223 cell line in the United States. *Id.* at 4, ¶ 18. TKT is the sponsor of the Investigational New Drug application for HMR4396. *Id.* at 4, ¶ 19.

B. *The Biological Activity of Erythropoietin*

As explained in the patent specification:

> Erythropoiesis, the production of red blood cells, occurs continuously throughout the human life span to offset cell destruction. Erythropoiesis is a very precisely controlled physiological mechanism enabling sufficient numbers of red blood cells to be available in the blood for proper tissue oxygenation, but not so many that the cells would impede circulation. The formation of red blood cells occurs in the bone marrow and is under the control of the hormone, erythropoietin.

Trial Ex. 1 at 5:39-47. In more basic terms, hemoglobin is the protein in red blood cells that transports oxygen. Trial Tr. at 1674:8-10. The amount of hemoglobin in the body correlates to the amount of oxygen that can be supplied to the body's tissues. *Id.* at 1674:11-14. Hematocrit is a measurement of the ability of the blood to supply oxygen to the body. *Id.* at 1674:15-17. Hematocrit level indicates the relative proportion of red blood cells to the total volume of blood. *Id.* at 1674:18-21. An increase or decrease in the hematocrit or hemoglobin results in an increase or decrease in the ability of the blood to supply oxygen to the body. *Id.* at 1674:22 to 1675:4. Under normal conditions, forty-five to fifty percent of the blood is made up of red blood cells, and in such circumstances, the hematocrit would be referred to as forty-five to fifty. *Id.* at 1570:24 to 1571:2.

Anemia occurs when a person does not have a steady, sufficient supply of red blood cells to carry oxygen to all the tissues of the body. *Id.* at 1674:4-7. Thus, the primary cause of anemia incident to chronic renal failure is a decrease in the production of red blood cells in the patient's blood. *Id.* at 1676:15 to 1677:5. The first medical condition for which erythropoietin was shown to be therapeutically effective as a pharmaceutical composition was this type of anemia. *Id.* at

2769:18-21. The therapeutic goal for treating patients with chronic renal failure is to increase and maintain the production of red blood cells in the patient's blood to normal or near normal levels. *Id.* at 1675:5-20. By increasing and maintaining the patient's hematocrit to normal or near normal levels, the ability of the patient's blood to provide a steady supply of sufficient oxygen to body tissues can be restored. *Id.* at 1681:11-15, 18-20. In order to correct the anemia incident to chronic renal failure, a sustained increase in hematocrit or hemoglobin to normal or at least near normal levels is required. *Id.* at 1681:18-20, 1688:25 to 1689:4. The therapeutic effectiveness or benefit of an erythropoietin preparation is shown by demonstrating a correction in anemia by increasing and maintaining the hematocrit of a patient to normal or near normal levels. *Id.* at 2763:4-8, 2777:14 to 2778:8. Measurements of hematocrit and hemoglobin were included in the first clinical trials involving recombinant erythropoietin ("rEPO") to allow physicians to determine if a treatment with erythropoietin had been effective. *Id.* at 1689:15-23. In those trials, rEPO was determined to be therapeutically effective because it was able to increase and maintain the patients' hematocrit level to thirty-five to forty percent. *Id.* at 2770:20-24, 2773:13-22, 2774:5-7. Furthermore, in conjunction with TKT's clinical trials of HMR4396 Injection, the FDA has rejected mere increases in hemoglobin as a meaningful therapeutic endpoint, and instead has insisted that TKT test for a sustained increase in hemoglobin over a minimum twelve-week period. *See* Trial Ex. 198; Trial Tr. 2254:8 to 2255:24.

C. *Judgment of Non-infringement of the '080 and '698 Patents*

Trial commenced on May 15, 2000. Following opening statements and pursuant to the schedule agreed upon during the April 18, 2000 final pretrial conference, *see* Fed. R. Civ. P. 16(a), Amgen began its infringement case. When Amgen

rested on the issue of infringement, TKT moved for judgment on partial findings, *see* Fed. R. Civ. P. 52(c), contending that (1) Amgen's infringement evidence was fatally deficient with respect to certain claims; and (2) judgment of non-infringement on those claims ought be issued. Following oral argument on June 9, 2000, the Court granted judgment of literal non-infringement with respect to the claims in suit of the '080 and '698 patents and judgment of non-infringement under the doctrine of equivalents with respect to the '698 patent. The factual findings[20] undergirding these conclusions are set forth below.

1. *'080 Patent*

On June 9, 2000, the Court found as matter of fact that there was no literal infringement of Claims 2, 3, and 4 of the '080 patent. In summary, the asserted claims of the '080 patent claim not only an erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, but also a pharmaceutical composition comprising a therapeutically effective amount of such glycoprotein.[21] In addition, the glycoprotein is further limited because in all the relevant claims it must comprise "the mature erythropoietin amino acid sequence of FIG. 6." Trial Ex. 3 at 38:42-43, 49-50. The Court had construed this highly significant phrase to mean "the fully realized form of the amino acid sequence

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[20] The Court made clear on the record that Amgen "introduced sufficient evidence as matter of law to warrant a finding by the Court of infringement." Trial Tr. at 1305:22-23. Thus, in subsequently finding that Amgen failed to persuade the Court by a fair preponderance of the evidence on these issues, the Court was acting entirely in its capacity as fact finder.

[21] Claims 2 and 3 are independent claims devoted to the erythropoietin glycoprotein, and Claim 4 is a dependent claim involving a pharmaceutical composition comprising the glycoprotein product according to Claims 2 and 3. Trial Ex. 3 at 38:39-53.

of Figure 6." Tr. of *Markman* Hr'g, Vol. II at 23:14-18. At the time of the *Markman* hearing, the determination of what, in fact, comprised the Figure 6 limitation was left for another day. *Supra* Section II.C, at 24-27. That day arrived when the Court was required to apply the claim construction to the factual record.

The patent specification's Figure 6 contains a significant amount of information on a number of levels that the parties do not dispute. Figure 6 displays the nucleotide series or DNA sequence of human erythropoietin including both exons (the portions of the sequence which code for the desired protein) and introns (the portions of the sequence that do not code for the protein and are spliced out during transcription into mRNA). *See* Trial Ex. 1 at 20:39 to 21:2. Figure 6 also sets apart a series of "codons," which are sets of three adjacent nucleotides that determine which of the twenty amino acids are incorporated into a protein at a particular location. Each amino acid is identified by its three letter abbreviation representing a codon. Figure 6 thus depicts the deduced amino acid sequence, which is arrived at by reading the codons of the DNA encoding the protein. Figure 6 also numbers the amino acids from -27 to 166. The span begins with a negative number because the negative amino acids represent the signal or leader peptide which is cleaved off in the rough endoplasmic reticulum prior to the protein's secretion from the cell. The numbers then continue from 1 to the final amino acid at position 166, which is labeled arginine. As will soon be apparent, it seems safe to say that never before has one arginine been so significant in a court of law.

Key language in the patent specification describes what is depicted by Figure 6: "FIG. 6 thus serves to identify the primary structural conformation (amino acid sequence) of mature human EPO as including 166 specified amino acid residues . . . ." *Id.* at 21:3-5. This language equates the amino acid sequence of mature human EPO with the specifically

enumerated 166 amino acid sequence that is disclosed in Figure 6. *Id.* In this light, it can scarcely be doubted that the "mature erythropoietin amino acid sequence" is the sequence depicted in Figure 6. Had Amgen claimed only "the mature erythropoietin amino acid sequence" without associating or linking that amino acid sequence to Figure 6 its argument that its claims cover whatever sequence (whether it contained 165 or 166 amino acids) is ultimately secreted by the cell might have more momentum. Yet because the asserted claims are limited explicitly by the meaning of Figure 6, the specific amino acid sequence displayed therein is significant. Amgen's attempt to persuade the Court that the claims reciting the amino acid sequence of Figure 6 reach the mature (i.e., fully realized or secreted) form of the protein, but are not further restricted by the specified amino acid sequence depicted in Figure 6 fails. As a result, in order to infringe Claims 2 and 3 of the '080 patent (and Claim 4 by dependence) literally, HMR4396 must contain an erythropoietin glycoprotein comprising the fully realized erythropoietin amino acid sequence of Figure 6, which depicts 166 amino acids.

With this claim construction, the Court turns to the trial testimony. During the trial, Dr. Harvey Lodish, a research biologist from the Whitehead Institute and the Massachusetts Institute of Technology, *see* Trial Tr. at 40:11-16, testified forthrightly about Figure 6 and specifically about the number of amino acid residues that comprise the erythropoietin protein. First, there is no dispute that the amino acids labeled 1 through 165 in Figure 6 are the same 1 through 165 that are contained in HMR4396. *Id.* at 202:14-16; *id.* at 348:10-12; Trial Ex. 25 at IND002357. During cross examination, however, Dr. Lodish and TKT's counsel had the following exchange:

> Q: You agree that Figure 6 displays an amino acid sequence of 166 amino acids?

A: It does. And—yes, it does. It certainly does.

Trial Tr. at 347:16-18. Dr. Lodish explained the discrepancy between Amgen's Figure 6 and the 165 amino acid sequence of the secreted EPO:

> What is missing is the arginine at position 166, and that is because, as I testified, that arginine is present on the initial protein made by the ribosomes in the cells and it is removed by the cell before the protein is secreted, and that is why I have 165.

Id. at 348:3-9. In fact, his testimony further reveals that at the time the patent was written, it was not yet known that the arginine at the carboxyl terminus was cleaved off prior to secretion of the protein from the cell. *Id.* at 350:20 to 351:4. But of particular importance in light of the Court's interpretation of Figure 6, during direct examination by Amgen's counsel, Dr. Lodish explained that "HMR4396 is a glycoprotein containing 165 amino acids." *Id.* at 200:21-22 (quoting Trial Ex. 18 at IND000019). Such a glycoprotein literally does not infringe a patent claim that specifies a 166 amino acid sequence. Consequently, at the close of Amgen's infringement case, the Court found that HMR4396 does not literally infringe Claims 2 and 3 (as well as Claim 4 by dependence) of the '080 patent.[22] *Id.* at 1306:19-23.

2. *'698 patent*

Also on June 9, 2000, the Court granted judgment of non-infringement with respect to the '698 patent, both literally and under the doctrine of equivalents. The asserted claims of the '698 patent address the process by which glycosylated erythropoietin polypeptides having certain characteristics are produced. Claims 4 and 6 are independent and Claims 5, 7, 8,

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[22] The Court denied the motion for judgment of non-infringement under the doctrine of equivalents on the '080 patent. *See* Trial Tr. at 1306:23-25.

and 9 are dependent. Because the Court was not persuaded by a preponderance of the evidence that TKT infringes Claims 4 and 6, judgment of non-infringement as to all of the asserted claims of the '698 patent is hereby entered.

In considering the '698 patent, the Court notes an important distinction between product patents on the one hand and process patents on the other. A product patent claims a structural entity that, though some process must be undertaken in order to create it, is in no way defined or limited by how it is made. *See Procter & Gamble Co.* v. *Berlin Mills Co.*, 256 F. 23, 29 (2d Cir. 1919); *Amgen, Inc.* v. *Chugai Pharm. Co., Ltd.*, 706 F. Supp. 94, 103 (D. Mass. 1989). A process patent, however, claims not a structural entity, "but rather an operation or series of steps leading to a useful result." 1 *Chisum on Patents* § 1.03, at 1-58 (2000). Thus, the very details regarding how such "useful result" has come about are at the heart of a process patent, whereas the process by which a patented product is obtained is ordinarily irrelevant to a product patent.

This distinction between product and process patents plays itself out in the context of the set of patents owned by Amgen and asserted in this litigation. The cells, glycoproteins, and pharmaceutical compositions protected by the '349, '933, '080, and '422 patents are all structural entities. They are therefore products and the patents that protect them are product patents. In contrast, the processes claimed in the '698 patent are different beasts all together. The claims of the '698 patent recite a series of steps that, if followed by one skilled in the art, will produce an identified useful result. Thus, unlike the product claims, for which it does not matter how one reached the patented result provided that the same (or substantially equivalent) result has been reached, *how one reaches the useful result* is the very substance of a process patent.

To put meat on these abstractions, compare the '349 patent with the '698 patent. Claim 1 of the '349 patent describes a

certain entity—a type of cell that has additional specific characteristics. In order to avoid infringing that product claim a competitor must not make that product regardless whether the process used to do so differs in some way from the process or processes described in the patent. If indeed the same product is ultimately obtained, it matters not that in order to do so the competitor tweaked the process in some manner. Of course, if the rule were any different, then product claims would easily be thwarted by even the most minuscule methodological modifications. Such a doctrine would render patent protection meaningless.

In contrast, *by its very nature as a process patent*, the '698 patent requires those skilled in the art to familiarize themselves with the details of the process for the production of recombinant glycosylated erythropoietin polypeptides. The process patent gives notice to competitors that the steps described therein are not to be repeated to achieve the same result. Thus, whereas in the product patent context, differences in process are meaningless, here, in the process patent context, these differences mean everything. Thus, in the '698 patent the devil is in the methodological details.

Based on this understanding of process patents, the many differences between Amgen's and TKT's processes, that were often admitted by Amgen's witnesses, rendered Amgen's proof of infringement on the '698 patent insufficient to survive TKT's Rule 52(c) motion. In short, the Court was not persuaded by a preponderance of the evidence that TKT's process for making GA-EPO (TKT's EPO product) infringed, either literally or by substantial equivalent, independent Claims 4 and 6 of the '698 patent. As a result, judgment of non-infringement will also be entered on dependent Claims 5, 7, 8, and 9. The Court now turns to these key methodological distinctions.

Among the variety of distinctions, two aspects of TKT's process stand out from Amgen's. First, and most funda-

mentally, TKT employs homologous rather than heterologous recombination. In order to make EPOGEN®, Amgen transfects Chinese hamster ovary ("CHO") cells with a vector that contains both viral promoter DNA and the human EPO gene. *See* Trial Ex. 1 at 25:55-61; Trial Tr. at 375:4-9. Thus, relative to the hamster host cell, the human EPO DNA material is exogenous because it has been removed from the cell in which it originated, placed in a vector, and reintroduced into a host cell. Trial Tr. at 174:18-22, 1330:2-5. In fact, the only type of recombination shown in Amgen's examples in the patent is heterologous. Trial Tr. at 375:19-25, 376:25 to 381:1. In order to make GA-EPO, however, TKT does not utilize a host cell from a non-human species. *See id.* at 165:19-21. Instead, TKT manipulates the human EPO gene where it naturally resides in an HT1080 human cell line. *Id.* at 165:21. In that sense then, the human EPO gene is endogenous to the human cell. *Id.* at 174:23 to 175:4. Thus, in TKT's process, after introducing a promoter sequence, human EPO is expressed in a human rather than hamster cell.

The Amgen patent specification's repeated references to exogenous DNA reveals that the Amgen process was directed toward heterologous rather than homologous recombination. The patent announces, for example, that "[t]hese polypeptides are also uniquely characterized by being the product of procaryotic or eucaryotic host expression (e.g., by bacterial, yeast and mammalian cells in culture) of exogenous DNA sequences obtained by genomic or cDNA [complementary DNA] cloning or by gene synthesis." Trial Ex. 1 at 10:15-20. The Amgen patent specifications also explain in summarizing what is depicted in Example 10 that:

> Example 10 is directed to a development of mammalian host expression systems for . . . human species genomic DNA involving Chinese hamster ovary ("CHO") cells and to the immunological and biological activities of

> products of these expression systems as well as characterization of such products.

Id. at 15:4-9. Here, Amgen makes plain that DNA material from one species and the cells from another have been utilized in order to effectuate expression. Amgen also specifically identified the content of the transfected vector, which included the human EPO gene, and the type of cell hosting the transfection, the CHO dihydrofolate reductase ("DHFR")[23] cells. *Id.* at 25:51-59. There can be no dispute that the process most heavily relied upon by Amgen in its patent is the transfection of exogenous DNA. This process, however, is not the one performed by TKT in making GA-EPO nor is it substantially similar to TKT's process. Instead, TKT is able to express high levels of human EPO in human cells without having to rely upon host cells from alternative species, an important distinction in the eyes of the Court.

A second distinction that the Court finds material to whether TKT's process infringes the two independent claims of the '698 patent concerns where the promoter DNA is located relative to the gene to be expressed. In the patent specification, Amgen described the exact location where the human EPO genetic fragment was cleaved in the process of creating the plasmid vector to be introduced into the host cell. *Id.* at 24:19-22. As explained in Example 7 and illustrated in Figure 4, Amgen created the vector by cleaving, with BstEII restriction endonucleases, within the 5.6 Kb EPO gene "at a position which is 44 base pairs 5' to the initiating ATG coding for the pre-peptide and approximately 680 base pairs 3' to the HindIII restriction site." *Id.* Dr. Lodish agreed that Amgen's endonucleases cleaved off genetic material at a position forty-four base pairs from the first codon that expresses the leader

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[23] The DHFR gene is a marker gene that allows for the selection of cells that have amplified copies of the gene.

peptide. *See* Trial Tr. at 372:14-19. Furthermore, the patent specification reports:

> The genomic human EPO gene can be isolated therefrom as a 4900 base pair BamHI digestion fragment carrying the complete structural gene with a single ATG 44 base pairs 3' to BamHI site adjacent the amino terminal coding region.

Trial Ex. 1 at 24:28-32. Thus, Amgen's process makes a point of leaving but one ATG in the region to be expressed. An ATG is often the codon where the ribosome attaches and where, therefore, protein synthesis initiates.

TKT, however, does something different. TKT inserts its CMV promoter and enhancer farther upstream than the position at which Amgen inserts its SV40 promoter. Thus TKT's process has within the DNA sequence upstream of the codons that express the EPO polypeptide several ATG sites. *See* Trial Tr. at 537:18-20. Despite the concern that these additional ATG sites might interfere with proper protein synthesis, TKT attaches its CMV promoter so many bases upstream that a number of these ATGs are present between the promoter and leader peptide. The Court finds that such a process is sufficiently different from that encompassed by Amgen's invention that judgment of non-infringement should follow.

In particular, the Court finds that the technique of placing the promoter in close proximity to the gene intended to be expressed was believed, by those of ordinary skill in the art in 1984, to be the technique most likely to result in the proper transcription of that gene. Amgen's patent itself teaches as much in Example 7. *See* Trial Ex. 1 at 24:15-32. Dr. Lodish's testimony does nothing to alter this conclusion. Dr. Lodish testified with respect to the promoter issue that "[w]hat is important is that if I put the SV40 promoter in this case, or perhaps other promoters, upstream of the EPO gene I will make EPO, and that's the critical issue." Trial Tr. at 549:

10-13. Yet, he shied away from definitively rejecting the idea that the location of the promoter relative to the desired gene was important. Instead, referring to the distance between the promoter and the gene to be expressed, he testified cautiously that "how far away from it, *perhaps* is not critical." *Id.* at 549:9-10 (emphasis added). Furthermore, Dr. Lodish seemed to be testifying, at least on this precise point, from his understanding of today's technology. He made no statement implying that one of ordinary skill in the art in 1984 would dare to place a promoter sequence in such a position that multiple ATGs would exist between it and the gene to be expressed. Thus, the process that Amgen described in its patent specification was one characterized by the placement of the promoter DNA in a position *adjacent* to the EPO leader peptide. Because TKT's process is more technologically advanced because it does not require the more immediate adjacency of the promoter, the Court finds that TKT's process for expressing the EPO protein in abundance is substantially different from the process identified in Amgen's '698 patent. As a result, Amgen has failed to prove by a preponderance of the evidence that TKT's process infringes the independent claims of the '698 patent.

Thus, because of TKT's use of both endogenous rather than exogenous DNA and a viral promoter located far upstream from the EPO coding region, as well as other less fundamental distinctions, TKT is entitled to judgment of non-infringement on the '698 patent both literally and under the doctrine of equivalents.

D. *Anticipation and Obviousness (Prior Art)*

After the Court rendered its findings and conclusions as to the partial judgment of non-infringement, TKT proceeded to present its case as to the remaining issues. At the conclusion of TKT's rebuttal case, Amgen moved for judgment of infringement and judgment of validity in separate motions. The motions were heard together on July 21, 2000, and at the

conclusion of the hearing, the Court made certain findings under Rule 52(c). While the Court declined to make any determinations on the remaining issues of infringement, Trial Tr. at 2532:7-8, the Court found that TKT had failed to carry its burden of proving its obviousness and anticipation defenses by clear and convincing evidence, *see id.* at 2534: 7-10. The required subsidiary findings and rulings follow.

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101. It comes as a surprise to no one that inventions must be new. "The novelty requirement lies at the heart of the patent system." 1 *Chisum on Patents* § 3.01, at 3-3. Section 102 helps to define this novelty requirement. It provides that:

> A person shall be entitled to a patent unless—
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention by the applicant for patent, or
>
> . . . .
>
> (e) the invention was described in—
>
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent . . . , or
>
> (g) (2) before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it . . . .

35 U.S.C. § 102. Thus, in order to negate the patent holder's claim of novelty by the use of prior art, one must show evidence of a prior patent or publication anywhere or prior use, knowledge, or invention in the United States. An invention is anticipated if it was known, used, patented, described,

or made by another prior to the applicant's invention thereof. *See* 1 *Chisum on Patents* § 3.02, at 3-6.

1. *Anticipation*

"[I]nvalidity by anticipation requires that the four corners of a single, prior art document describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Advanced Display Sys., Inc.* v. *Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) (citing *Atlas Powder Co.* v. *Ireco Inc.*, 190 F.3d 1342, 1347 [Fed. Cir. 1999]; and *In re Paulsen*, 30 F.3d 1475, 1479 [Fed. Cir. 1994]). The identical invention must be shown in a single prior art reference in as complete detail as contained in the patent. *Richardson* v. *Suzuki Motor Co., Ltd.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). Furthermore prior art reference must be enabling, thus placing the claimed invention in the possession of the public. *Akzo N.V.* v. *United States Int'l Trade Comm'n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986). "Anticipation, put simply, requires that every element of the claimed invention was previously 'described in a single reference.'" *Advanced Display*, 212 F.3d at 1283 (quoting *Scripps Clinic & Research Found.* v. *Genentech, Inc.*, 927 F.2d 1565, 1576 [Fed. Cir. 1991]). Moreover, if the Patent Office considered a particular prior art reference, then the challenger has the "added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job." *Am. Hoist & Derrick Co.* v. *Sowa & Sons, Inc.*, 725 F.2d 1350, 1359 (Fed. Cir. 1984); *see Ultra-Tex Surfaces, Inc.* v. *Hill Bros. Chem. Co.*, 204 F.3d 1360, 1367 (Fed. Cir. 2000).

Determining whether a prior art reference has anticipated a patented invention is matter of fact. *Advanced Display*, 212 F.3d at 1283. TKT bears the burden of proving invalidity by anticipation by clear and convincing evidence. *Robotic Vision Sys.* v. *View Enq'g, Inc.*, 189 F.3d 1370, 1377 (Fed. Cir.

1999). Clear and convincing evidence is "evidence which produces in the mind of the trier of fact an abiding conviction that the truth of [the] factual contentions is 'highly probable.'" *Buildex, Inc.* v. *Kason Indus., Inc.*, 849 F.2d 1461, 1463 (Fed. Cir. 1988).

a. *EPO-Producing Human Tumor Cells*

TKT contended that the cells described in a series of references anticipate certain Amgen claims because the references describe human tumor cells that produce EPO.[24] Among these nine references are Kaname Sugimoto's United States Patent No. 4,377,513 (the '513 patent), which identifies a process for the production of human erythropoietin from lymphoblastoid cells,[25] and an article by Masamichi

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[24] These are the references: J.L. Ascensao et al., *Erythropoietin Production by a Human Testicular Germ Cell Line*, 62 Blood 1132-34 (1983) (Trial Ex. 2425); Masamichi Hagiwara et al., *Erythropoietin Production in Long-term Cultures of Human Renal Carcinoma Cells*, 154 Exp. Cell Res. 619-24 (1984) (Trial Ex. 2428); Tsunehiro Saito et al., *Translation of Messenger RNA from a Renal Tumor into a Product with the Biological Properties of Erythropoietin*, 13 Exp. Hematol. 23-28 (1985) (Trial Ex. 2427); T. Saito et al., *Translation of Human Erythropoietin-mRNAs*, 11(14) Exp. Hematol. 228 (1983) (Trial Ex. 2426); Judith B. Sherwood & Daniel Shouval, *Continuous Production of Erythropoietin by an Established Human Renal Carcinoma Cell Line: Development of the Cell Line*, 83 Proc. Nat'l Acad. Sci. USA 16569 (1986) (Trial Ex. 2424); J.B. Sherwood et al., *Establishment of a Human Erythropoietin-Producing Renal Carcinoma Cell Line*, 31 Clinical Res. 163A (1983) (Trial Ex. 2432); Kaname Sugimoto, *Process for the Production of Human Erythropoietin*, United States Patent No. 4,377,513 (issued Mar. 22, 1983) (Trial Ex. 2374); Tomoyuki Tajima, Japanese Patent Application Kokai Number: SHO 54-55790 (1979) (Trial Ex. 2423); Keisuke Toyama et al., *Erythropoietin Levels in the Course of a Patient With Erythropoietin-Producing Renal Cell Carcinoma and Transplantation of This Tumor in Nude Mice*, 54 Blood 245-53 (1979) (Trial Ex. 2249).

[25] A lymphoblastoid cell is a cell typically isolated from a patient with leukemia, which is a cancer of the blood. Trial Tr. at 1795:20-22.

Hagiwara et al., which reports the isolation of erythropoietin from human renal carcinoma cells. *See* Trial Exs. 2374, 2428. Dr. Erslev, a witness proffered by TKT, agreed that the remaining seven references report cells that are essentially the same as those identified in Hagiwara's report, *see* Trial Tr. at 1743:21 to 1744:18. After examining these references, the Court agreed with Dr. Erslev. In each case, the researchers surgically removed tumor tissues from cancer patients who had high levels of EPO production, and then cultured those cells in order to try to detect erythropoietic activity. *See* Trial Exs. 2249, 2423-27, 2432. Amgen's patent specification specifically disclosed the Sugimoto patent and identified another article by Hagiwara that reported the same results. Trial Ex. 1 at 7:24-42.

Amgen's disclosure of two references that are representative of the work in this area gives rise to the notion that "the burden of proving invalidity is especially heavy" when the defendant relies on "art that has previously been considered by the patent office during prosecution of the patent application." *Pall Corp.* v. *Micron Separations, Inc.*, 792 F. Supp. 1298, 1314 (D. Mass. 1992), *aff'd in part, rev'd in part*, 66 F.3d 1211 (Fed. Cir. 1995); *see Am. Hoist*, 725 F.2d at 1359. Although this burden is not insurmountable, TKT failed to overcome it.

First, the Court considered whether these references constituted "prior art." Amgen submitted that two of these nine references failed to satisfy the touchstone element of the prior art defense: that the art was in fact prior. Amgen argued that the "printed publication" of the references was subsequent to Amgen's date of invention. *See* 35 U.S.C. § 102(a). The 1986 Sherwood and Shouval reference concerning production of EPO in human renal carcinoma cells was published years after the time necessary to be considered a prior art publication. Trial Ex. 2424; *see* 35 U.S.C. § 102(b). Likewise, the Saito et al. reference regarding EPO

activity in renal tumor cells grown in culture was published in 1985, Trial Ex. 2427, a year after the last of Amgen's patent applications was submitted to the Patent Office. While the document does bear the words, "Received 18 August 1983; accepted 18 July 1984," *id.*, TKT has failed to persuade the Court that either of these earlier dates should be considered the appropriate date of the "printed publication." 35 U.S.C. § 102(a). To qualify as a "printed publication" under section 102, a party must show accessability and availability to those skilled in the art. *Carella* v. *Starlight Archery & Pro Line Co.*, 804 F.2d 135, 139 (Fed. Cir. 1986). The fact that a reference was received by a publication does not evidence that it was either available or accessible. Consequently, neither of these articles constitute a prior art publication.

Yet as the statute makes clear, there is more than one way to skin the prior art cat. If the invention is made, used, or known in the United States prior to invention by the patent holder, then it has been anticipated. 35 U.S.C. § 102(a), (g). Thus, the fact that the 1985 Saito et al. and 1986 Sherwood and Shouval references were published after the filing of Amgen's patent applications does not alone render the work described in those references inadequate for anticipation purposes. Instead, the Court finds that the Sherwood and Shouval and Saito et al. references evidence that the work performed by the researchers was done in the United States prior to Amgen's breakthroughs in late 1983 and 1984. *See* Trial Exs. 2424, 2427. The Sherwood and Shouval reference reports that their human renal carcinoma cell line had maintained its EPO-producing function continuously since 1981. Trial Ex. 2424 at 165. Though it is not explicitly mentioned in the article, the Court infers from Dr. Sherwood's Bronx, New York business address that her work was performed in the United States. *Id.* Similarly, the work reported in the 1985 Saito et al. reference appears to have been performed at the University of Tennessee College of

Medicine in Knoxville sometime prior to August of 1983. Trial Ex. 2427 at 23.

Beyond the fact that the work appears to have been performed somewhere in the United States prior to Amgen's work, the knowledge or use of the work must also be accessible to the public. *See Carella*, 804 F.2d at 139. "A prior use is sufficient to anticipate a patent if it involves work done openly and in the ordinary course of business activities without any deliberate attempt at concealment or effort to exclude the public, even though no deliberate act was taken to bring the work to the attention of the public at large . . . ." *State Indus., Inc.* v. *Rheem Mfg. Co.*, No. 3-83-0362, 1984 WL 1243, at *18 (M.D. Tenn. June 5, 1984), *aff'd in part, rev'd in part*, 769 F.2d 762 (Fed. Cir. 1985) (reversing on inequitable conduct and award of attorneys fees). Rather than requiring widespread public use or knowledge, section 102(a) only requires courts to examine whether prior inventors made deliberate efforts to conceal (or otherwise exclude the public from) their inventive work. *See W.L. Gore & Assocs., Inc.* v. *Gorlock, Inc.*, 721 F.2d 1540, 1550 (Fed. Cir. 1983). If they did not, and instead performed their work openly and in the ordinary course of business, then their use (and by implication, knowledge) should be considered accessible to the public. *See Elec. Storage Battery Co.*, v. *Shimadzu*, 307 U.S. 5, 20 (1939); *Baxter Int'l, Inc.* v. *COBE Lab., Inc.*, 88 F.3d 1054, 1058 (Fed. Cir. 1996). Because the record contains no evidence to suggest that Saito or Sherwood and their colleagues took any actions to shield their work from others, the Court finds that the knowledge and use of the work that was subsequently described in the two references meets the requirements of section 102(a). As a result, the EPO-producing tumor cell work described by the Sherwood and Shouval and Saito et al. references qualifies as prior art, though it remains to be seen whether this art anticipates any of Amgen's claims.

The second step in an anticipation analysis involves a comparison of the construed claim to the prior art. A prior art reference must disclose "each and every limitation of the claimed invention . . . must be enabling[,] and [must] describe . . . [the] claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention." *In re Paulsen*, 30 F.3d at 1478-79.

After comparing the construed claim with the 1983 Saito et al. reference, the 1983 Sherwood et al. reference, and the never-issued patent application of Tajima, Trial Exs. 2426, 2432, 2423, the Court was unpersuaded that the references described or enabled "the claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention." *Helifix Ltd* v. *Blok-Lak, Ltd.*, 208 F.3d 1339, 1346 (Fed. Cir. 2000); *see Advanced Display Sys., Inc.* v. *Wu*, 212 F.3d 1272, 1282 (Fed. Cir. 2000). Further, TKT failed to elicit persuasive testimony from its witnesses that showed that one of ordinary skill in the art could produce Amgen's cells after examining any of these references. Moreover, although not dispositive, these references were never scrutinized by the scientific community. Both the 1983 Sherwood et al. and 1983 Saito et al. references were simply abstracts and were not peer reviewed prior to publication. Absent the close and careful scrutiny afforded by such review, the abstracts lack significant persuasive punch. Similarly, the unexamined, never-issued Tajima patent constitutes nothing more than unchallenged scientific claims. In contrast, an issued patent stands on far more solid footing because it has been scrutinized and challenged by an examiner trained in the field in which the patent teaches.

To further support its anticipation defense, TKT relies most heavily on Sugimoto's '513 patent. *See* Trial Ex. 2374. Recall that the '513 patent, as well as Sugimoto's related work, was disclosed in Amgen's patent specification. *See* Trial Ex. 1 at 7:24-35. In light of the subsequent issuance of Amgen's

patents, the Patent office clearly concluded that this reference was not anticipating. Nonetheless, it was open to TKT to persuade the Court that the examiner erred. Ultimately, however, TKT could not carry its burden of proof by clear and convincing evidence.

The '513 patent describes a process for the production of human EPO from human lymphoblastoid cells. Trial Ex. 2374 at 1:21-26. More precisely, Sugimoto teaches that if a human cell line that produces EPO is fused with a human lymphoblastoid cell line, the resulting fused cells produce significant amounts of EPO. Trial Tr. at 1226:21 to 1227:7, 1797:10-19. Sugimoto also advises that (1) conventional techniques can be utilized to achieve purification; and (2) the human EPO produced thereby can be used in pharmaceutical compositions for the treatment of anemia. Trial Ex. 2374 at 3:51 to 4:2. During the *Markman* hearing, counsel for Amgen admitted that its patent covered subject matter that included Sugimoto's work, but counsel also explained that Amgen distinguished Sugimoto during prosecution on the basis that Sugimoto "didn't succeed in actually making a cell that was capable of producing EPO." Tr. of *Markman* Hr'g, Vol. III at 50:1-7. Not surprisingly then, Amgen countered TKT's contention that Sugimoto anticipated Amgen's invention by arguing that Sugimoto was not enabled.

Amgen's contention was supported by trial testimony. On cross examination, Dr. Erslev agreed that the Sugimoto process was "very complex" and that he was "flabbergasted" when he first read Sugimoto's procedure. Trial Tr. at 1754:24 to 1755:9. According to Dr. Erslev, no one had attempted to use Sugimoto's process to produce erythropoietin prior to 1984 despite significant financial incentives to do so. *See id.* at 1755:10-12. Furthermore, according to Dr. Erslev, no one reported using Sugimoto's process to make a pharmaceutical composition of human EPO, nor has any patient ever been treated by any EPO produced by the Sugimoto procedure. *Id.*

at 1755:17 to 1756:3. In light of the intense competition that grew out of the race to make human EPO suitable for treatment of chronic anemia, one would imagine that if Sugimoto's invention were truly enabling, then he would have won that lucrative race.

To counter, TKT proffered its Vice President of Molecular Biology, Dr. Michael Heartlein, who testified regarding experiments he performed in which he fused a lymphoblastoid cell with a human cell producing EPO and studied the results of these fused, or hybrid cells. *Id.* at 1791:12-20, 1795:13-17. In addition to using TKT's EPO-producing HT1080 cells, Dr. Heartlein selected two types of liver carcinoma cells as his EPO producing cells, HepG2 and Hep3B cells. *Id.* at 1798:12-21. In the presence of polyethylene glycol ("PEG"), which causes the destablilization of the cell membranes, the contents of the two cells were mixed together. Once PEG is removed, the membranes resealed, forming the fused or hybrid cells. *Id.* at 1799:17-22. After fusing the cells, Dr. Heartlein cloned out individual cell lines from the pool of fused cells, *see id.* at 1800:11-13, and then quantified the EPO in each of these clones using a commercially available EPO immunoassay, *see id.* at 1801:14-18. He found approximately a six-fold increase in EPO production rates in the cloned cells compared to that of the parental EPO producing cells. *Id.* at 1802:6-7, 1803:15-17. Thus, Dr. Heartlein concluded that he was "able to isolate hybrid cells between a lymphoblastoid cell and a human cell producing EPO, and . . . found that the majority of the clones that were isolated were producing more EPO than the original . . . human cell producing EPO." *Id.* at 1796:12-16. His testimony was intended to show that Sugimoto's process could be performed with routine experimentation and would produce results similar to those reported by Sugimoto. Yet Dr. Heartlein's procedures suffer from a series of deficiencies.

First, Dr. Heartlein could not identify any clones producing EPO in fusions involving the HepG2 cells. *Id.* at 1803:18 to 1804:3, 1829:19-21. Because Sugimoto's patent is not limited to certain types of EPO-producing cells, Trial Ex. 2374 at 6:64-65 (describing "human cells capable of producing human erythropoietin"), the failure to produce EPO from a lymphoblastoid/HepG2 hybrid cell alone indicates that Sugimoto's patent is not enabled. *Genentech, Inc.* v. *Novo Nordisk, A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). In fact, the only fused cells that were successful in producing EPO were those that were produced with HT1080 cells that had been altered by the addition of a nonhuman promoter. Trial Tr. at 1830:1-4. These cells, however, were not available in 1983. *Id.* at 1831:9-11.

Second, Dr. Heartlein's process diverged in a number of ways from that taught by Sugimoto. Whereas Sugimoto's patent only addresses growing up his lymphoblastoid cells in vivo, Dr. Heartlein used only in vitro processes. *Id.* at 1809:14 to 1810:5. Additionally, unlike the EPO-producing cells utilized by Dr. Heartlein, Sugimoto actually used and disclosed minced human kidney tumor cells. *Id.* at 1812:10 to 1813:3. Though he searched, Dr. Heartlein was unable to obtain such cells. *Id.* at 1813:4-13. Dr. Heartlein was also unable to obtain any of the lymphoblastoid cells that are identified in the patent. *Id.* at 1816:2-14. Because he could not obtain the same starting materials as Sugimoto, Dr. Heartlein could not directly repeat any of Sugimoto's examples. *Id.* at 1819:18-23. Thus, TKT provided no evidence adequate to overcome the presumption that the Patent Office correctly rejected the contention that Sugimoto was an anticipating reference. TKT's evidence merely confirms that rejection. Consequently, TKT has failed to show by clear and convincing evidence that Sugimoto's '513 patent anticipated the Amgen patent.

Furthermore, none of the cited references disclose each and every limitation of any of Amgen's individual claims. *Helifix*, 208 F.3d at 1346. As to Claim 1 of the '422 patent, none of the cited references describe a therapeutically effective amount of EPO or the purification of human EPO from mammalian cells grown in culture. Additionally, all but two of the sources (Sugimoto's patent and Tajima's patent application) fail to mention the potential use of EPO generated from hybrid cells in a pharmaceutical composition. Because these references do not describe each claim limitation of Claim 1 of the '422 patent, they do not anticipate that claim.

Similarly, none of the references anticipate the '349 patent. Independent Claims 1 and 4 of the '349 patent are not anticipated by any of these references because none of them disclose the use of non-human DNA sequences that control transcription. Furthermore, other than Sugimoto's patent, none of the references describe the cells as capable of producing in the medium of their growth in excess of 100 units of EPO per 10^6 cells. In addition, neither the Toyama et al. nor Sugimoto references discuss in vitro propagation of their hybrid cells. Because these references fail to disclose essential elements of the relevant claims, they do not anticipate the '349 claims.

Likewise, none of the references anticipate the '933 patent. Because these references fail to address glycosylation of the EPO glycoproteins produced from their hybrid cells, they simply do not describe (1) any differences in glycosylation between their proteins and urinary EPO proteins, as required by Claim 1 of the '933 patent; or (2) any molecular weight comparisons with human urinary EPO as required by Claim 2 of the same patent. In addition, all of the references fail to examine the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells. Thus, because the references do not disclose each and every limitation of the '933 claims, they do not anticipate the '933 patent.

The same conclusion arises with respect to the '080 patent. Each asserted claim makes reference to the mature erythropoietin amino acid sequence of Figure 6 which, of course, is unique to the Amgen patent. In fact, as Dr. Lodish explained, the sequence disclosed in Figure 6 is at the heart of Amgen's invention. None of the cited references discuss in any way the amino acid sequence of human erythropoietin. Moreover, as previously mentioned with respect to the '933 claims, all of the references fail to examine the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, which is a limitation contained in all three asserted claims of the '080 patent. Thus, because none of these references disclose each element of any specific asserted claim in this litigation, these references do not anticipate any of Amgen's claims.

b. *Prior Administration of Raw Plasma*

TKT also failed to show by clear and convincing evidence that Dr. U. Essers' raw plasma preparation references meet each and every limitation of Amgen's claims.[26] *See* Trial Exs. 2415-17. The three references report experiments performed by Dr. Essers whereby a small group of both anemic and healthy patients received infusions of erythropoietin-rich plasma. *See id.* Dr. Essers had to use raw human plasma because, at the time she performed her work, there was no erythropoietin available in the quantity and purity required for therapeutic use. Trial Tr. at 1709:4-10. Dr. Essers reported

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[26] These are the three references: U. Essers et al., *Effect of Erythropoietin in Normal Men and in Patients with Renal Insufficiency*, 11 European Dialysis & Transplant Ass'n Proc., Biomed W1 EU715, 398-402 (1975) (Trial Ex. 2417); U. Essers et al., *Weitere Untersuchungen zur Wirksamkeit von Erythropoietin bei Patienten mit Niereninsuffizienz*, 99 Deutsche Medizinische Wochenschrift, 1618-24 (1974) (Trial Ex. 2415); U. Essers et al., *Zur Wirkung von Erythropoietin bei Gesunden und bei Patienten mit chronischer Uramie*, 51 Klinische Wochenschrif 1005-09 (1973) (Trial Ex. 2416).

that many of the patients showed an increase in their reticulocyte counts. *See* Trial Exs. 241517; Trial Tr. at 1555:20 to 1556:7. Yet despite this increase in the reticulocytes, Dr. Essers saw no improvement in the more meaningful measurement of hematocrit or hemoglobin levels of her patients. *See* Trial Ex. 2415; Trial Tr. at 1710:21-25, 1712:7 to 1713:13. In the "Open Discussion" portion of the document published after the European Dialysis and Transplant Association Proceedings, Dr. Essers participated in the following exchange:

> LEBER You have demonstrated that after erythropoietin infusion reticulocytes increased in uraemic patients. Was this accompanied or followed by an increased haemoglobin haematocrit value, and erythrocyte count as well. Or was it only an increase in the reticulocyte count?
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> ESSERS There was only an increase in the absolute reticulocyte count. I think this was due to the fact that we did not have enough erythropoietin to give the patient to stimulate an increase in haemoglobin.

Trial Ex. 2417 at 401-02. Dr. Essers never proved that anemia could be corrected using her raw plasma preparation. Trial Tr. at 1714:21-23. Thus, while Dr. Essers may have been successful in elevating the reticulocyte counts of some of her patients, the failure to initiate and sustain an increase in the hematocrit or hemoglobin levels reveals that the Essers' work did not meet Amgen's therapeutic effectiveness standard. *See* Trial Ex. 2 at 39:1-4, Trial Ex. 3 at 38:51-53, Trial Ex. 6 at 38:36-41 (pharmaceutical composition claims of '933, '080, and '422 patents, respectively). As a result, Dr. Essers' references do not anticipate the pharmaceutical composition claims.

The references fail to meet other limitations of Amgen's various claims as well. Because the raw plasma was drawn from human blood, Trial Exs. 2415-17, Dr. Essers' EPO product could not be said to be non-naturally occurring, as is

required by Claim 1 of the '933 patent, Trial Ex. 2 at 36:17, and Claim 3 of the '080 patent, Trial Ex. 3 at 38:45. In addition, because the EPO glycoprotein is not isolated from the plasma preparation, the Essers' preparation does not satisfy the first limitation of Claim 2 of the '080 patent. *See id.* Trial Ex. 3 at 38:39-44. Moreover, like the tumor cell references, Dr. Essers' articles do not address glycosylation or molecular weight differences and, therefore, do not anticipate either Claim 1 or Claim 2 of the '933 patent. *See* Trial Ex. 2 at 38:17-24. With respect to the '422 patent, in addition to its failure to provide a therapeutically effective amount of human erythropoietin, Dr. Essers' plasma preparation is not purified from mammalian cells grown in culture, as it is drawn from human blood. Trial Ex. 6 at 38:37-41. Thus, the references regarding Dr. Essers' plasma preparation work fail to anticipate any of the claims asserted by Amgen.

c. *Prior Administration of Urinary EPO*

In support of its anticipation defense, TKT also relies upon a clinical study performed under the direction of Dr. Eugene Goldwasser. As an initial matter, Amgen again challenges whether this study constitutes prior art under 35 U.S.C. § 102. For the same reasons that the Court rejected Amgen's attack on the 1985 Saito et al. and 1986 Sherwood and Shouval experiments, the Court rebuffs this attack as well. Because the documents submitted as exhibits in this case reveal that Dr. Goldwasser began this clinical study in 1979-1980 at the University of Chicago in Illinois, *see* Trial Ex. 2055, it could fairly be said that it predates Amgen's patent application. *See* 35 U.S.C. § 102(a), (g). That it appears to be prior art is only part of the analysis, for the only prior art that renders Amgen's claims invalid is that which anticipates Amgen's claims. In order to make that determination, one must understand what it is Dr. Goldwasser accomplished.

Dr. Goldwasser obtained a preparation of highly purified erythropoietin derived from human urine. Trial Ex. 2055. Then, in the clinical study, approximately 10,000 units (in dosages of 500 and 1000 units) of human urinary EPO was administered to three anemic patients. Trial Ex. 2057 at 19; *see also* Trial Tr. at 1579:5-9. Dr. Goldwasser observed a number of biologic effects in the patients. He reported an increase in reticulocyte count in all three patients, an increase in erythroid cells in the marrow and an increased plasma iron clearance rate in two patients, and an increase in red cell mass in one patient. *See* Trial Ex. 2057 at 19. Testifying about Dr. Goldwasser's work, Dr. Erslev explained that these "results . . . indicate very strongly that the patients did respond by having an increase in the rate of red cell production." Trial Tr. at 1578:4-6. According to Dr. Erslev, the increase in (1) the reticulocytes; (2) the plasma iron clearance rate; and (3) the red blood cell mass are all "strong evidence for an increase in the rate of red cell production." *Id.* at 1578:10-12; *see id.* at 1578:7 to 1579:2. Dr. Erslev also conceded that an increase in reticulocytes alone does not correct a patient's anemia. *Id.* at 1688:14 to 1689:4.

Importantly, however, Dr. Goldwasser admits that "[t]here was no significant change in hematocrit in any patient," Trial Ex. 2057 at 19, and Dr. Erslev agreed that the accepted standard by which physicians measure a therapeutic response to EPO is an increase in hematocrit, *see* Trial Tr. at 1675:12-23. Due to this lack of effect upon hematocrit levels, the patients did not appear to receive any health benefits from the reported biologic effects. *See id.* at 1719:7-21, 1720:11-13, 1919:4-12. Furthermore, Dr. Goldwasser himself has testified that his abortive, three-patient trial was a failure. *See* Goldwasser Dep. at 317:14 to 321:2. Consequently, the Goldwasser study could not anticipate any of Amgen's claims requiring a therapeutically effective amount of EPO. As the Federal Circuit explained in *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549 (Fed. Cir. 1985), "another's experiment, imperfect and never perfected

will not serve either as an anticipation or as part of the prior art, for it has not served to enrich it." *Id.* at 1558 (quoting *Picard* v. *United Aircraft Corp.*, 128 F.2d 632, 635 [2d. Cir. 1942]). Such is the case here.

In order to refute Dr. Goldwasser's downplaying of his own work, TKT points to statements made by him and Dr. Baron, the researcher working on the project under Dr. Goldwasser's direction, which were made shortly after the experiments. Dr. Baron reported to the FDA that "[d]efinite evidence of erythroid marrow stimulation was detected." Trial Ex. 2058 at 2. Dr. Goldwasser also explained in his National Institute of Health grant application that EPO "can have a physiological effect in this type of anemia." Trial Ex. 2057 at 19. First, these statements do not contradict the conclusion that the clinical study was limited, in the sense that only three patients participated, and abortive, in the sense that sufficient amounts of urinary EPO material was not readily accessible to continue it. Second, while urinary EPO may have had some "physiological effects" including "erythroid marrow stimulation," such effects serve as only evidence of the stimulation of red blood cell production. Such evidence should be outweighed by the fact that the *actual* production of mature red blood cells was not achieved and, as a result, hematocrit levels were unchanged.[27] Because an increase in hematocrit and hemoglobin levels is the true mark of therapeutic effectiveness, Dr. Goldwasser's study, which

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[27] Failure to increase hematocrit levels may have been caused by the fact that the potency of Goldwasser's urinary EPO was less than half that of recombinant EPO. *See* Trial Ex. 137 at 699; Trial Tr. at 1742:3-23. Likewise, the failure to stimulate the production of mature red blood cells may have been caused by the fact that, compared to recombinant EPO, Goldwasser's uEPO cleared from circulation rapidly. *See* Trial Ex. 2058 at 1; Trial Tr. at 1097:8-14, 1102:5-22, 1741:10-12. Regardless of the reason, it is clear that Goldwasser's work did not effect a change in hematocrit. Trial Ex. 2058 at 2 (reporting that no increase in hematocrit level was observed).

revealed only inchoate indicators of red blood cell production, falls far short of anticipating claims requiring a therapeutic amount of human EPO. Thus, the study does not anticipate the pharmaceutical composition claims of the '933, '080, and '422 patents. Likewise, because Goldwasser's work failed to stimulate production of red blood cells as well as reticulocytes, the study does not anticipate Claim 1 of the '933 patent and Claims 2 and 3 of the '080 patent.

Furthermore, the Goldwasser study fails to address many of the additional aspects of Amgen's claims. For example, Amgen specifically excluded urinary EPO preparations from the scope of the claims by including the claim limitation "non-naturally occurring" and "not isolated from human urine." Trial Ex. 2 at 38:17; Trial Ex. 3 at 38:44. The purification of EPO from patients with anemia, whose urine often has a high volume of EPO, constitutes an example of naturally-occurring EPO. Thus, Claims 1 and 2 of the '933 patent and Claims 2 and 3 of the '080 patent simply do not encompass Dr. Goldwasser's urinary EPO treatment. *See* Trial Ex. 2 at 3:17-25; Trial Ex. 3 at 38:39-50. Likewise, because Dr. Goldwasser's work does not pertain to cells that have been altered by recombinant means in order to express high levels f EPO, it does not implicate any of the claims of the '349 patent. Trial Ex. 5 at 38:7-14, 18-27, 31-37. Because Dr. Goldwasser's work cannot satisfy these claim limitations, it cannot anticipate Amgen's claims.

2. *Obviousness*

A patent is invalid if the differences between the patented subject matter and the prior art are such that the patented subject matter as a whole would have been obvious at the time of the invention to a person having ordinary skill in the art. 35 U.S.C. § 103(a). Whether an invention is obvious is a legal conclusion based upon underlying factual inquiries. *See Graham* v. *John Deere Co.*, 383 U.S. 1, 17-18 (1966). As in all other invalidity analyses, the party asserting an obvious-

ness defense must prove the disputed facts by clear and convincing evidence. *See Ga.-Pac. Corp.* v. *United States Gypsum Co.*, 195 F.3d 1322, 1330 (Fed. Cir. 2000).

"Obviousness rests on several critical factual underpinnings: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of skill in the art; and (4) the objective indicia of nonobviousness." *Yamanouchi Pharm. Co., Ltd.* v. *Danbury Pharm., Inc.*, 231 F.3d 1339, 1342 (Fed. Cir. 2000); *see also Graham*, 383 U.S. at 17-18. Among the relevant objective, secondary considerations are: (1) copying; (2) long-felt, but unresolved need; (3) the failure of others; (4) commercial success; (5) unexpected results created by the claimed inventions; (6) unexpected properties of the claimed inventions; (7) licenses revealing industry respect for the invention; and (8) skepticism of skilled artisans before the invention. *See In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998). Although secondary considerations must be weighed, they do not control the determination of obviousness. *See Richardson-Vicks, Inc.* v. *Upjohn Co.*, 122 F.3d 1476, 1483 (Fed. Cir. 1997) ("Evidence of secondary considerations [is] but a part of the 'totality of the evidence' that is used to reach the ultimate conclusion of obviousness.").

Unlike the defense of anticipation, which requires a *single* prior art reference to contain each and every limitation of the claimed invention, the defense of obviousness may be made out where it would be obvious to one of ordinary skill in the art to *combine* the teachings of more than one prior art source in order to accomplish the claimed invention. The Federal Circuit, however, has made clear that the elements of this "combination theory" require "a showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential evidentiary component of an obviousness hold-

ing.'"[28] *Brown & Williamson Tobacco Corp.* v. *Philip Morris Inc.*, 229 F.3d 1120, 1125 (Fed. Cir. 2000) (quoting *C.R. Bard, Inc.* v. *M3 Sys. Inc.*, 157 F.3d 1340, 1352 [Fed. Cir. 1998]). Such "evidence may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved." *Id.* (citing *Pro-Mold & Tool Co.* v. *Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 [Fed. Cir. 1996]). The Federal Circuit has made clear that the showing must be by clear and convincing evidence. Specifically, the showing must be clear and particular, and broad conclusory statements about the teaching of multiple references, standing alone, are insufficient. *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999), *abrogated on other grounds by In re Gartside*, 203 F.3d 1305 (Fed. Cir. 2000). Furthermore, the alleged infringer must show that one of ordinary skill in the art would reasonably expect that combining the teachings of myriad sources would achieve success. *Yamanouchi*, 231 F.3d at 341 (citing *In re Longi*, 759 F.2d 887, 896 [Fed. Cir. 1985]); *Ortho Pharm. Corp.* v. *Smith*, 959 F.2d 936, 942 (Fed. Cir. 1992).

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[28] The Federal Circuit has recently reiterated the importance of the motivation to combine requirement:

> As this court has stated, "virtually all [inventions] are combinations of old elements." Therefore, an [accused infringer] may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an [accused infringer] to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention.
>
> . . . .
>
> To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

In re Rouffet, 149 F.3d at 1357-58 (internal citations omitted).

TKT first argued that the Sugimoto patent rendered a number of Amgen's claims invalid due to obviousness. A prior art reference must be enabling, however, which thereby places the claimed invention in the possession of the public. *See Akzo N.V.* v. *United States Int'l Trade Comm'n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986). In addressing the defense of anticipation, the Court found that the Sugimoto patent was not enabled and, therefore, that it had no effect upon the validity of Amgen's patents. *Supra* Section IV.D.1.a, at 84-89. Because TKT failed to prove that Sugimoto was enabled,[29] Sugimoto is not prior art, and therefore it cannot support TKT's obviousness defense.

Second, TKT relied upon Dr. Goldwasser's urinary EPO preparation as a potential base from which to launch an obviousness sortie. Because Dr. Goldwasser's study was a failure, *see* Goldwasser Dep. at 317:14 to 321:2, the Court already concluded that Dr. Goldwasser's work did not constitute prior art, *supra* Section IV.D.1.c, at 94-98. In addition, particularly where the lead scientist implicitly revealed his disappointment by aborting the work, it seems clear that a person of ordinary skill in the art would not reasonably have expected that Dr. Goldwasser's work would eventually bear fruit. Instead, the more reasonable conclusion would be that

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[29] Had the Court concluded otherwise, however, the Sugimoto patent would go a long way toward proving TKT's obviousness defense. As explained above, Sugimoto disclosed EPO-producing fused cells and advised that (1) conventional techniques can be utilized to achieve purification and (2) the human EPO produced thereby can be used in pharmaceutical compositions for the treatment of anemia. Trial Ex. 2374 at 3:51 to 4:2. Thus, the patent itself suggested combining its invention with prior art sources relating to both purification and therapeutic delivery. Provided that one of ordinary skill in the art could actually make the EPO-producing cells described in the Sugimoto patent, a point on which TKT failed to persuade this Court, such a combination of prior art materials might render invalid the pharmaceutical composition claims of the '933, '080, and '422 patents.

a urinary EPO preparation would remain unsuccessful in treating anemia despite its stimulation of some preliminary biologic effects.

As against the claims of the '349 patent, TKT points to the various EPO-producing human tumor cell references identified above, *see supra* note 24. Yet all of these references fail to render obvious any of the '349 claims because of one important distinction. The two independent claims of the '349 patent describe cells comprising (1) "non-human DNA sequences that control transcription of DNA encoding human erythropoietin"; or (2) "transcription control DNA sequences, other than human erythropoietin transcription control sequences." Trial Ex. 5 at 38:13-14, 22-23. The references do not describe cells comprising these DNA elements, nor could one of ordinary skill in the art make the cells claimed in the '349 patent with the knowledge provided by the tumor cell references. The key knowledge that the art lacked prior to Amgen's disclosure was EPO's genetic sequence. Without identifying the sequence of the DNA encoding human erythropoietin, one of ordinary skill in the art would be unable to hook up transcription control sequences in a way that caused transcription of the EPO gene. The cells claimed in the '349 patent are distinct not only because of the high volume of EPO they are capable of producing, but also because of the cells' unique genetic makeup. The tumor cell references do not speak to these genetic characteristics nor would any knowledge possessed by those of ordinary skill in the art in 1983-1984 fill this gap. Moreover, there is no clear evidence that these prior art tumor cells produced EPO in the medium of their growth in excess of 100 or 1000 U of erythropoietin per 10^6 cells in forty-eight hours. While producing EPO in such abundance was indeed one of the primary goals of researchers at that time, that goal continued to escape their grasp. Even with knowledge of these prior art cells, those of ordinary skill at that time simply did not have the ability to induce greater EPO production from these cells

or from other sources of EPO for that matter. Thus, having cells that showed some EPO production was a far cry from having cells that produced EPO to the degree claimed in the '349 patent. Consequently, the Court finds that TKT has failed to show by clear and convincing evidence that the tumor cell references render the '349 claims obvious.

Third, TKT contended that the human tumor cell references could be combined with the work of Drs. Essers or Goldwasser as well as the purification work of Yanagawa or Chiba to defeat the validity of Amgen's pharmaceutical composition claims. *See* Trial Exs. 2055-56, 2058, 2231, 2252, 2415-17. A number of the tumor cell references and the Yanagawa reference were explicitly disclosed by Amgen during the patent prosecution. Trial Ex. 1 at 7:63 to 8:15. The Court infers that the Patent Office, therefore, contemplated this question and decided in favor of nonobviousness. Importantly, TKT failed to prove the existence of any suggestion in the prior art to combine these references so as to produce the pharmaceutical compositions claimed in the '933, '080, and '422 patents. Furthermore, the Court is not persuaded that one of ordinary skill in the art could have used the Yanagawa or Chiba purification methods to purify to substantial homogeneity the EPO produced in the tumor cell cultures. Likewise, the evidence was insufficient to warrant the conclusion that plasma EPO could be purified to homogeneity. The fact that no one has ever—then or now—attempted to determine if a pharmaceutical composition comprising human EPO could be made from these cultured prior art cells also informs the Court's decision. Trial Tr. at 1750:23 to 1751:14, 1753:17 25; 1755:10 to 1756:3. In light of all these facts, the contention that these various references could be combined to produce a pharmaceutical composition meeting the limitations of Claim 9 of the '933 patent, Claim 4 of the '080 patent, and Claim 1 of the '422 patent is simply unsubstantiated conjecture.

Finally, the secondary considerations in this case are telling. *See Pall Corp.* v. *Micron Separations, Inc.*, 792 F. Supp. 1298, 1316 (D. Mass. 1992) ("Objective evidence of non-obviousness may well be the most pertinent probative and revealing evidence available to aid in reaching a conclusion with respect to [the] issue [of obviousness.]") (citations omitted), *aff'd in part, rev'd in part*, 66 F.3d 1211 (Fed. Cir. 1995); *see also Richardson*, 122 F.3d at 1483. Dr. Erslev testified at length about the repeated failures of researchers around the world who were attempting to create an EPO product effective in treating patients with anemia. *See, e.g.*, Trial Tr. at 1650:8 to 1651:12, 1657:4-13, 1657:19 to 1658:3, 1658:12 to 1659:1, 1709:410, 1710:15-20, 1712:7 to 1714:20, 1715:15 to 1716:25. Throughout the 1970s, researchers sought to conduct clinical studies with EPO to determine its therapeutic effectiveness, but such trials were hampered by a lack of supply of EPO from natural sources. *Id.* at 1651:22 to 1652:18. Thus, Dr. Erslev explained that the need for the mass production of EPO had existed for "many, many, many years." *Id.* at 1673:14-21. Additionally, in light of the complications associated with the then existing forms of treatment for the anemia of chronic renal failure, there was a need for an alternative therapy. *Id.* at 1669:6 to 1670:13. Indeed, until the advent of Amgen's recombinant EPO product, the anemia associated with chronic renal failure remained uncorrected. *See id.* at 1659:2 to 1666:25, 1667:15 to 1668:10, 1669:1-5, 1720:14-17. The results of the first clinical trials with recombinant human EPO were "dramatic beyond anyone's dreams." *Id.* at 1665:10 to 1667:4. Before the advent of Amgen's product, whether EPO could actually produce a sustainable increase in a patient's hematocrit was not known. *Id.* at 1579:22 to 1580:19, 1656:11-18, 1669:1-9, 1720:11-17. Furthermore, Amgen's EPO product, which was the first EPO-containing pharmaceutical composition to obtain FDA approval, has greatly improved the quality of life of chronic renal failure patients throughout the world. *Id.* at 1671:16 to

1673:3. As a result, Dr. Lin received widespread public acclaim for his work. Trial Exs. 156-58; Trial Tr. at 981:17 to 982:6, 984:8 to 985:10.

From these uncontested factual conclusions, it is but a short hop to infer that, prior to Amgen's pathbreaking invention, there was a long-felt need for a human EPO preparation that was therapeutically effective in treating the anemia of chronic renal failure. Despite researchers all across the globe seeking to fulfill that need (and commercial entities desperately hoping to capitalize on it), Amgen was the first to succeed. Amgen's invention opened the floodgates for EPO production and ultimately led to a therapeutically effective pharmaceutical composition containing human EPO. One cannot help but wonder if achieving such an outcome by combining certain known prior art techniques were truly obvious to those of ordinary skill in the art, why didn't one of the myriad competitors do it? Consequently, the Court finds that the secondary considerations strongly counsel the Court against a finding of obviousness.

Thus, having considered the scope and content of various prior art references, the differences between such references and the claimed inventions, how one skilled in the art might combine such references in order to make what was claimed by Amgen, and the objective, secondary considerations, the Court concluded that TKT failed to persuade the Court by clear and convincing evidence that Amgen's inventions were obvious in light of prior art. As a result, pursuant to Rule 52(c), the Court granted judgment of validity with respect to the defense of obviousness.[30] *See* Trial Tr. at 2534:7-10. The

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[30] The Court's ruling had one exception, however. Trial Tr. at 2534:7-22. The Court permitted TKT to present additional evidence with respect to whether the examiner was unaware of material information that may have colored the examiner's view of the relationship between the prior art and Amgen's claimed inventions. *Id.* at 2534:10-18. In light of the Court's findings with respect to TKT's inequitable conduct defense, *see infra*

Court declined to make any further rulings regarding TKT's validity defenses.

Following the Court's Rule 52(c) prior art determinations, the Court undertook to receive Amgen's rebuttal evidence regarding TKT's validity defenses and also received testimony, offered by TKT, from attorneys involved in the prosecution of Amgen's patents. When all the evidence had been received, the Court entertained closing arguments and took the remaining issues under advisement. Beginning with the question of infringement, the latter portion of this memorandum resolves these issues.

E. *Infringement*

Proof of infringement may be made out pursuant to either of two theories: literal infringement or the doctrine of equivalents. In determining whether an accused product literally infringes a patent claim, the Court applies a two-step analysis. *CAE Screenplates, Inc.* v. *Heinrich Fiedler GMBH & Co. KG*, 224 F.3d 1308, 1316 (Fed. Cir. 2000). First, the claims must be construed to determine the scope of the claims. *Id.*; *see also Kahn* v. *Gen. Motors Corp.*, 135 F.3d 1472, 1476 (Fed. Cir. 1998). Second, the claims must be compared to the accused product. *CAE Screenplates*, 224 F.3d at 1316; *Kahn*, 135 F.3d at 1476. If the accused product meets each of the limitations contained in a claim, then the product literally infringes that claim. If, however, even one limitation is not met, then the product does not literally infringe. A plaintiff in the latter circumstance is not without a remedy and, therefore, the defendant is not yet out of the woods. "A device which does not infringe a patent claim literally may still infringe the claim under the doctrine of equivalents if each and every

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Section IV.F.1, at 166-94, the Court holds that TKT's evidence adds nothing to its prior art defense. Consequently, the Court rejects in toto TKT's claim that Amgen's inventions were either anticipated by or obvious in light of prior art sources.

limitation of the claim is literally or equivalently present." *CAE Screenplates*, 224 F.3d at 1318-19 (citing *Pennwalt Corp.* v. *Durand-Wayland, Inc.*, 833 F.2d 931, 934-35 [Fed. Cir. 1987]). A claim limitation is equivalently present in an accused product if there are only "insubstantial differences" between the limitation and the corresponding aspects of the product. *Hilton Davis Chem. Co.* v. *Warner-Jenkinson Co.*, 62 F.3d 1512, 1517-18 (Fed. Cir. 1995), *rev'd on other grounds*, 520 U.S. 17 (1997). "The usual test of the substantiality of the differences is whether the element in the accused composition performs substantially the same function in substantially the same way to obtain substantially the same result as the claimed element." *Upjohn Co.* v. *Mova Pharm. Corp.*, 225 F.3d 1306, 1309 (Fed. Cir. 2000); *see also Graver Tank & Mfg. Co.* v. *Linde Air Prods. Co.*, 339 U.S. 605, 608 (1950). "The application of infringement by equivalents, however, is limited by the doctrine of prosecution history estoppel." *CAE Screenplates*, 224 F.3d at 1319; *see also Festo Corp.* v. *Shoketso Kinzoku Kogyo Kabushiki Co., Ltd.*, No. 95-1066, 2000 WL 1753646, at *3 (Fed. Cir. Nov. 29, 2000). Prosecution history estoppel "provides that a patent owner can be estopped from relying upon the doctrine of equivalents when the patent applicant relinquishes coverage of subject matter during the prosecution of the patent, either by amendment or argument." *CAE Screenplates*, 224 F.3d at 1319; *Pharmacia & Upjohn Co.* v. *Mylan Pharms., Inc.*, 170 F.3d 1373, 1376-77 (Fed. Cir. 1999). With this legal framework in mind and having already construed a number of key terms, the Court turns its face "to the stormy seas [of infringement] and bids the land farewell." Tommy Makem, *Ballad of the Lady Jane*, *on* Lonesome Waters (Shanachie Records Co. 1993).

1. *The '349 Patent*

As matter of fact, the Court finds that TKT's R223 cells meet each of the limitations of Claims 1, 3, 4, and 6 of the

'349 patent. A number of subsidiary factual findings relevant to this patent have already been made on the summary judgment record. First, the Court ruled on March 28, 2000 that R223 cells are vertebrate cells. Tr. of *Markman* Hr'g, Vol. II at 136:3-4. The admission by TKT's counsel during the *Markman* hearing that R223 cells are vertebrate cells under the Court's construction, i.e. cells from an animal having a backbone, is sufficient to warrant a factual finding in that regard. *Id.* at 131:5-6. Second, TKT's Rule 30(b)(6) designee, David S. Johnson, testified at his deposition that R223 cells are vertebrate cells. Galvin Decl. (Nov. 4, 1999) Ex. 4 at 76:12-14. In short, the R223 cell line is derived from the HT1080 cell line which is, in turn, derived from a cancerous human cell. Thus, the cell is from an animal having a backbone—a human. Trial testimony by Dr. Kingston during Amgen's cross examination—though unnecessary in light of the summary judgment determination—bolsters this finding. Trial Tr. at 1380:25 to 1381:16. Third, the Court ruled that R223 cells are capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of 100 units of erythropoietin per 10^6 cells in forty-eight hours as determined by radioimmunoassay ("RIA").[31] Dr. Ronald W. McLawhon's second declaration was very influential in this determination. In particular, after performing RIAs with TKT's R223 cells, which yielded erythropoietin in amounts far in excess of 100 units per 10^6 cells in forty-eight hours, Dr. McLawhon concluded that R223 cells were capable of producing more than 1000 units of human erythropoietin per 10^6 cells in forty-eight hours. *See* McLawhon Decl. (Mar. 3, 2000) at 8, ¶ 23. TKT produced no evidence refuting the implications of Dr. McLawhon's RIA tests. Again, though such evidence is unnecessary

[31] RIA is a widely used technique for quantifying the amount of a protein in a sample. Binding of an antibody to the protein of interest allows for the identification of that protein.

in light of the Court's summary judgment determination, substantial evidence introduced at trial supports this ruling. *See* Trial Ex. 14 at HMR 336545; Trial Ex. 19 at IND000568; Trial Tr. at 277:7 to 279:5, 1473:12-25. Fourth, the Court ruled on the summary judgment record that the R223 cell line contains non-human DNA sequences that control transcription. The R223 cells contain the cytomegalovirus ("CMV") promoter, a viral (and therefore, nonhuman) DNA sequence that initiates transcription. Galvin Decl. (Nov. 4, 1999) Ex. 4 at 98:11-14, 129:23 to 130:13, 134:3-25. The CMV promoter is not derived from the human genome. *Id.* Ex. 3 at 37:21-22. This CMV promoter is present in R223 cells and initiates the transcription of sequences that encode human erythropoietin. *Id.* Ex. 5 at 438:19 to 439:2, 480:3-13. Finally, the IND displays a schematic diagram of the vector used by TKT, known as the targeting construct pREPO22, which depicts the CMV promoter "used for initiation f the GA-EPO mRNA transcript . . ." *Id.* Ex. 12 at IND000788. In light of the evidence presented by Amgen and not refuted by TKT, the Court ruled on summary judgment that the R223 cell line contains nonhuman DNA sequences that control transcription. Upon further reflection, however, the Court modifies its summary judgment determination. The evidence on the summary judgment record was sufficient to show that the CMV promoter *initiates* transcription, but upon reflection was insufficient to prove that the CMV sequence also *regulates* transcription. Under the Court's construction, both actions are necessary in order to "control" transcription. Neither party has been prejudiced by this modification for, as is seen below, this issue was the subject of much testimony during trial.

As to the remaining limitations in Claim 1 of the '349 patent, the Court ruled that a trial was necessary in order to determine whether the R223 cells literally infringe. After hearing evidence on these matters, the Court now finds as matter of fact that the R223 cells meet the remaining limitations in Claim 1. First, the R223 cells can be propagated

in vitro. Joint Pretrial Mem. at 5, ¶ 23. Second, R223 cells contain a DNA sequence that not only initiates transcription, but also regulates transcription of DNA encoding human erythropoietin. In particular, the R223 cells contain CMV enhancer sequences that regulate transcription of DNA encoding human erythropoietin by determining the rate at which RNA polymerase binds and makes an RNA copy of the DNA encoding human EPO. *See* Trial Ex. 19 at IND000559, Trial Ex. 20 at IND000829-30. As Dr. Harvey Lodish explained, a regulatory DNA sequence called an enhancer not only binds proteins that interact physically with RNA polymerase, but also increase the ability of RNA polymerase to bind to the promoter sequence. Trial Tr. at 106:11 to 107:2. Thus, "a strong enhancer would be one which would initiate or cause RNA polymerase to initiate transcription at a very high rate." *Id.* at 107:3-5. Dr. Lodish subsequently testified that TKT's CMV sequence contains several strong enhancers that are capable of binding proteins that determine the frequency or rate of transcription initiation of DNA encoding human EPO. *Id.* at 271:11-17. Dr. Lodish firmly based his opinion not only on his review of the relevant literature, but also on TKT's own IND submissions. *Id.* at 271:11 to 276:10. Similarly, Dr. Robert E. Kingston admitted on cross-examination that the R223 cells contain CMV enhancer sequences. *Id.* at 1384:2-3. He agreed that the CMV enhancer sequences are capable of attracting or binding certain proteins that can affect the rate or frequency of transcription initiation. *Id.* at 1393:16-22. Dr. Kingston also agreed that the CMV enhancer sequences are positioned in the R223 cells at a location so as to affect the rate or frequency at which RNA transcripts that include the EPO DNA are formed. *See id.* at 1393:23 to 1394:9. As a result, the Court now finds that the CMV enhancer DNA sequences regulate transcription of DNA encoding human EPO. Thus, in conjunction with its summary judgment ruling that the CMV promoter initiates transcription of EPO DNA, the Court finds that the R223

cells contain non-human DNA sequences that control transcription of DNA encoding human erythropoietin.

Thus, the Court finds as matter of fact that TKT's R223 cells (1) are vertebrate cells that can be propagated in vitro; (2) are capable, upon growth in culture, of producing erythropoietin in the medium of their growth in excess of 100 units of erythropoietin per 10^6 cells in forty-eight hours as determined by RIA; and (3) contain non-human DNA sequences that control transcription of DNA encoding human erythropoietin. Consequently, the defendants' R223 cells literally infringe Claim 1 of the '349 patent.

Dependent Claim 3 of the '349 patent differs from Claim 1 only in that it specifies that the vertebrate cells be capable of producing in excess of 1000 units of EPO per 10^6 cells in forty-eight hours as opposed to the 100 units specified in Claim 1. Trial Ex. 5 at 38:18-20. The trial evidence on this point is somewhat circuitous, for Amgen relies on data obtained from an enzyme-linked immunosorbent assay ("ELISA")[32] as opposed to a RIA. The terms of Claim 3, however, fail to specify the test by which the amount of EPO must be measured. Furthermore, the Court sees no reason why it should incorporate the RIA limitation of Claim 1 into dependent Claim 3. Claim 3's dependence upon Claim 1 requires certain elements of Claim 1 to be satisfied in order to infringe Claim 3. Yet Claim 3 introduces a heightened standard for EPO production that is not limited by the method of measurement. Thus, Claim 3 can be literally infringed upon evidence that the infringing cells produce the required amount of EPO as measured by tests other than RIAs. Nevertheless, even if the Court were to hold that radioimmunoassays were required under Claim 3, Amgen's evidence regarding the comparability of ELISA and RIA measurements would more

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[32] Although similar to RIA, ELISA uses a different method of identifying the protein of interest.

than support the Court's finding of infringement under the doctrine of equivalents. A summary of the relevant evidence follows. First, TKT's IND discloses that the R223 cells are capable of producing 2118 units of EPO per 10^6 cells per day when grown in culture as measured by an ELISA assay. *See* Trial Ex. 19 at IND000568, 000842. Furthermore, the ELISA and RIA assays provide comparable measures of EPO activity because, in each test, the results are normalized to a known amount of EPO. Trial Ex. 14 at HMR 336545; Trial Tr. at 278:17 to 279:5, 1473:12-25. As a result, the R223 cells are capable of producing in excess of 1000 units of EPO per 10^6 cells in forty-eight hours when grown in culture. *See* Trial Ex. 14 at HMR 336545; Trial Ex. 19 at IND000568; Trial Tr. 277:7 to 279:5, 281:12-19, 1473:12-25. Thus, either literally or under the doctrine of equivalents, the Court finds that the R223 cells infringe Claim 3 of the '349 patent.

Claim 4 of the '349 patent differs from Claim 1 in the phraseology describing the transcription control DNA sequences. Whereas Claim 1 specifies vertebrate cells "comprising non-human DNA sequences that control transcription of DNA encoding human erythropoietin," Trial Ex. 5 at 38:12-14, Claim 4 claims vertebrate cells "which comprise transcription control DNA sequences, other than human erythropoietin transcription control sequences, for production of human erythropoietin." *Id.* at 38:22-24. Claim 4 actually describes a larger subset of claimed transcription control sequences than Claim 1 because it sweeps within its reach not only all non-human DNA sequences, but also all human DNA sequences other than human EPO transcription control sequences. Despite this distinction in the claim language, the same factual finding results. The CMV DNA sequences in R223 cells are not human erythropoietin control sequences. A CMV is a virus whose DNA material is not naturally found on the human genome. *See* David Johnson Designated Dep. at 98:8-14. The CMV DNA sequences, therefore, are not human. Because the CMV DNA sequences are not human,

they cannot possibly be human erythropoietin transcription control sequences. *See* Trial Ex. 18 at IND000017; Trial Ex. 20 at IND000790. The trial testimony of Dr. Lodish and Dr. Kingston, in addition to the exhibits and testimony referred to regarding Claim 1, *see* Trial Tr. at 282:12 to 283:6, 296:20 to 298:14, 299:21 to 300:5, 1409:4-25, and designated deposition testimony amply supports this finding, *see* David Johnson Designated Dep. at 96:8 to 98:14, 129:5 to 130:7; Treco Designated Dep. at 446:24 to 447:2, 478:9 to 479:14 (explaining that the CMV immediate early gene has transcription control sequences that control transcription of the DNA sequences that encode gene activated erythropoietin). In light of such admissions and the other evidence presented during the course of trial, the Court is persuaded that R223 cells contain transcription control DNA sequences, other than human erythropoietin transcription control sequences, for production of human erythropoietin. Consequently, the Court finds as matter of fact that TKT's R223 cells literally infringe Claim 4 of the '349 patent.

Claim 6 of the '349 patent depends upon Claim 4, but differs, just as Claim 3 differs from Claim 1, in the amount of units of EPO that the cell is capable of producing. Trial Ex. 5 at 38:31-33. Having already determined both that the R223 cells are capable of producing in excess of 1000 units of EPO per 10^6 cells in forty-eight hours when grown in culture and that the R223 cells meet the other limitations of Claim 4, nothing more need be said. Thus, based on the evidence discussed above underlying the factual findings regarding Claims 3 and 4 of the '349 patent, the Court finds as matter of fact that the R223 cells infringe Claim 6 of the '349 patent.

In determining that the R223 cells infringe Claims 1, 3, 4 and 6 of the '349 patent, the Court necessarily rejected all of TKT's infringement defenses. The most plausible, but ultimately unavailing contentions, are considered here. TKT primarily attempts to distinguish its cells on the basis of the

origin of the human EPO DNA contained therein. Indeed, it is true that Amgen inserts the EPO DNA by transfection into the non-human host cell, whereas TKT's human cell already contains the human EPO DNA. Yet this factual distinction is immaterial because the claim language is not limited by the origin of the EPO DNA. In short, Amgen only had to show and actually showed that the DNA that the non-human transcription control DNA sequences controlled was the DNA encoding human EPO. *See, e.g.*, Trial Tr. 270:4 to 271:6, 276:15 to 277:1, 1393:5 to 1394:9. This is all it needs to show on this point. Whether the DNA encoding human EPO originated within or outside f the host cell simply does not matter.

Even if TKT's distinctions were sufficient to defend against literal infringement, it could not have defended against the doctrine of equivalents given Amgen's proffered evidence. Dr. Lodish explained that because the two distinct cells have the same sequence within the coding region, the origin of the DNA is immaterial, and precisely the same glycoprotein is produced in terms of structure and biological activity.[33] Trial Tr. at 174:18 to 175:18; *see also id.* at 175:1-18, 303:3-15, 1376:15 to 1378:8, 1448:2 to 1451:9 (explaining that the fact that TKT's R223 cells produce EPO from DNA that is endogenous rather than exogenous to the host cell does not alter the structure or the glycosylation of the EPO protein that is ultimately secreted by the R223 cell). Furthermore, TKT admitted to the FDA that its clinical trials show that HMR4396 produced from vertebrate cells con-

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[33] Dr. Kingston's testimony during cross-examination, though more constrained than Dr. Lodish's, supports Dr. Lodish's opinion on this narrow point. On cross-examination, Dr. Kingston testified that "[t]here are nonhuman DNA sequences in [TKT's] cells which work together with human DNA sequences in [TKT's] cells to control transcription." Trial Tr. at 1409:7-9; *see also id.* at 1376:15 to 1377:19, 1448:7 to 1449:10, 1450:11 to 1451:9.

taining endogenous human EPO DNA and EPOGEN® produced from vertebrate cells containing exogenous human EPO DNA are equivalent in their therapeutic properties. Trial Ex. 122 at HMR 801225, 801231, 801281; Trial Ex. 123 at HMR 801510; Trial Tr. at 492:8 to 493:1. A subsequent pharmaceutical manufacturer may argue to the FDA that its product is as safe or as effective as another product already on the market, but it ought not be permitted to run from its earlier representations once the matter of patent infringement comes its way.

The Court also finds that the chromosomal location of the DNA encoding EPO as well as the genomic environment surrounding the EPO DNA is irrelevant to the infringement analysis of the '349 claims, and therefore, TKT's attempts to distinguish its cells on these bases is simply misguided. TKT's evidence in this regard seems to be offered for the purpose of showing that its cells are somehow less engineered (and more natural) than Amgen's. Yet without making any determination regarding whether these distinctions even exist, the Court concludes that nothing in the claim language of the '349 claims calls for these distinctions. As a result, the Court deems both TKT's evidence supporting these contentions and Amgen's rebuttal evidence on these issues (including Dr. Tlsty's flourescent in situ hybridization ["FISH"] analysis data with respect to the R223 cells) immaterial.

Finally, and importantly, the fact that the R223 cells contain the endogenous human EPO promoter and regulatory elements does not matter. The term of art "comprise" or "comprising" as used in Claims 1 and 4 is not meant to indicate that an exhaustive list is following. Instead, it merely means that the object of the phrase—in this case, the cells—contains at least (though not exclusively) the item or items listed thereafter. While the specified elements following "comprise" and "comprising" are essential, additional elements may be added to the specified elements and still form a

construct within the scope of the claim. *Genentech, Inc.* v. *Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997). Thus, it matters not that the endogenous EPO promoter and enhancer sequences are present, as long as the cells contain the non-human (Claim 1) or other than human (Claim 4) EPO promoter sequences. Because the R223 cells do, they infringe Claims 1, 3, 4, and 6 of the '349 patent.

Amgen also contends that TKT infringes Claim 7 of the '349 patent. Unlike the other claims of the '349 patent, Claim 7 is directed to a process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, the claimed vertebrate cells. While the methods employed by TKT to reach the result protected by Amgen's cell product claims are immaterial to the infringement analysis of those cell product claims, such methods are crucial with respect to Claim 7. *See supra* Section IV.C.2, at 66-74 (regarding the judgment of non-infringement of the '698 patent).

In light of this, the Court concludes that Amgen has failed to prove by a preponderance of the evidence that TKT's process for the production of erythropoietin infringes Claim 7. As described in more detail with respect to the ruling of non-infringement of the '698 patent, *see supra* Section IV.C.2, at 6874, TKT's process for producing erythropoietin differs markedly from that disclosed by Amgen's specification. Of particular significance, TKT (1) utilizes the endogenous rather than exogenous EPO gene; and (2) places its promoter upstream from rather than adjacent to the EPO gene. *See* Trial Ex. 1 at 24:1922, 24:28-32, 25:55-61; Trial Tr. at 165:19-21, 174:18 to 175:4, 372:14-19, 375:19-25, 376:20 to 381:1, 537:18-20, 1330:2-5. Thus, relying on the same reasoning that gave rise to the non-infringement ruling with respect to the '698 patent, the Court here finds that TKT does not infringe literally or under the document of equivalents Claim 7 of the '349 patent. Nevertheless, judgment of

infringement will enter with respect to Claims 1, 3, 4, and 6 of the '349 patent.

2. *The '933 Patent*

Claim 1 of the '933 patent is directed to non-naturally occurring EPO glycoprotein products having both the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and glycosylation which differs from that of human urinary EPO. Trial Ex. 2 at 38:17-21. Each claim limitation and the evidence relating thereto is considered seriatim.

First, the Court finds that HMR4396 is "non-naturally occurring," which the Court interpreted as meaning "not occurring in nature" or "would not occur but for human intervention," *see supra* Section II.H, at 36-39. One technique contemplated by this claim limitation is recombinant DNA technology which in simple terms, consists of linking two DNAs that are not normally together. Trial Tr. at 129:5-6. A construct consisting of two recombined DNA sequences is not naturally occurring in the sense that but for human intervention, they would not exist together in a DNA strand. *Id.* at 128:4 to 129:3. Moreover, any glycoproteins obtained from transcription of recombinant DNA and translation of the resulting mRNA as well as the pharmaceutical composition derived therefrom, are non-naturally occurring.

The evidence is clear that HMR4396 is only made by manipulation of R223 cells which would not otherwise naturally produce EPO. In fact, TKT's witness, Dr. Kingston testified directly that "the EPO region in [TKT's) R223 cells is non-naturally occurring, yes." *Id.* at 1417:20-21; *see also* Treco Designated Dep. at 505:20 to 506:4 (recognizing that R223 cells are not found in nature). Dr. Kingston also agreed that the HT1080 cells used to make the R223 cells do not naturally produce EPO. Trial Tr. at 1503:8-12. In addition, Dr. Tlsty specifically described the dramatic changes she

discovered upon comparing R223 cells with their parent HT1080 cells through karyotypic and FISH testing. *Id.* at 844:21 to 847:7, 858:21 to 859:4, 882:12-20. Her tests revealed that the EPO DNA located on chromosome 7 of the HT1080 cells had been replicated, significantly rearranged, and scattered throughout various segments of chromosomal material within R223 cells. *See* Trial Exs. 90, 151-54. The inference suggested by her testimony and accepted by the Court is that the condition of the R223 cells could not have happened without human intervention—most importantly TKT's amplifying the EPO DNA within the R223 cells. Thus, the Court finds that HMR4396 is non-naturally occurring as that claim is employed in the '933 patent.

Second, the Court finds that HMR4396 is an erythropoietin glycoprotein product, as is required by the claim. A protein is a linear molecule usually consisting of more than fifty amino acids linked together in a specific sequence. Proteins form the key structural elements in cells and participate in nearly all cellular activities. As the name suggests, a glycoprotein is a protein that has undergone glycosylation,[34] a process whereby groups (or chains) of carbohydrate (or sugar) residues chemically attach to the protein as the protein is synthesized.[35] Thus, in order for HMR4396 to constitute an erythropoietin glycoprotein product, it must contain the EPO protein and that protein must have chemically attached carbohydrate chains. Such is the case here. In fact, TKT admitted during the *Markman* hearing that its product "is an erythropoietin polypeptide that has glycosylation . . . ." Tr. of *Markman* Hr'g, Vol. II at 134:14-15. Furthermore, in light of

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[34] The process of glycosylation is discussed in more detail below. *See infra* Section IV.E.2, at 129-32.

[35] As explained by one expert in the field of glycobiology, "the word glyco is really of Greek origin . . . from the word glykys, meaning sweet, and it's been used for many, many years to denote anything having to do with carbohydrates and carbohydrate structure." Trial Tr. at 569:17-20.

the substantial amount of trial time devoted to the specific glycosylation characteristics of HMR4396, there can be no doubt that HMR4396 is an erythropoietin glycoprotein product.

Third, HMR4396 meets the claim limitation that the glycoprotein product have "the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells." Trial Ex. 2 at 38:18-20. In the Amended Answer, TKT explained that in preliminary animal testing, its product had "the *in vivo* biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells." Am. Answer ¶ 26. Then, during the *Markman* hearing, in response to the Court's question whether HMR4396 "causes bone marrow cells to increase production of reticulocytes and red blood cells in vivo," counsel for TKT admitted, "The answer to that is yes." Tr. of *Markman* Hr'g, Vol. II at 134:1720. In light of these admissions, the Court finds that HMR4396 literally infringes the claim limitation requiring the EPO glycoprotein to have the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells.

The fourth and final claim limitation is the stickiest. Claim 1 of the '933 patent claims an EPO glycoprotein "having glycosylation which differs from that of human urinary erythropoietin." Trial Ex. 2 at 38:20-21. The Court has construed the phrase "glycosylation which differs" to mean "glycosylation as to which there is a detectable difference based upon what was known in 1983-1984 from that of human urinary erythropoietin, having in mind that the patent holder, Amgen, taught the use of this Western blot, SDS-PAGE and monosaccharide test." Tr. of *Markman* Hr'g, Vol. III at 102:15-23. Thus, in order for Amgen to prove literal infringement on this point, the claim language requires evidence that persuasively establishes detectable differ-

ences between the glycosylation of TKT's product and the glycosylation of human urinary EPO.

Amgen put forth Dr. Richard D. Cummings, a professor of biochemistry and molecular biology at the University of Oklahoma Health Center in Oklahoma City, to testify regarding glycosylation. Trial Tr. at 560:21 to 561:1. Dr. Cummings explained that glycosylation is directed by the complement of enzymes that cells contain as well as the structure of the protein itself. *Id.* at 576:4-9. Proteins are often depicted in a linear fashion by their amino acid sequence, *see, e.g.*, Trial Ex. 1 Fig.6, but in reality, proteins are naturally folded, Trial Tr. at 576:9-10. As a result, the folded protein may be more or less accessible to the various enzymes that affect glycosylation. *Id.* at 576:10-15. Just as the expression of proteins is regulated genetically by DNA, the expression of the enzymes that place carbohydrates on proteins is also genetically regulated. *Id.* at 576:18-21. Thus, DNA directs certain cells not only to express certain proteins, but also to express specific enzymes that act upon those proteins. In particular, the enzymes known as glycosyltransferases transfer sugars from a donor onto the protein. *Id.* at 577:17-22. This process is what is referred to as "glycosylation."

In 1983, there were a number of analytical techniques available for detecting differences in glycosylation between different glycoproteins. *Id.* at 578:13-17. One such technique was known as SDS-PAGE. *Id.* at 578:20-24, 581:16. In order to perform SDS-PAGE experiments, the protein of interest is incubated with a detergent called sodium dedecyl sulfate, which binds to the protein, denatures it so that it is more or less linearized, and contributes a strong negative charge to the protein. *Id.* at 581:14-20. The protein is then placed in an SDS-PAGE apparatus that contains an electric field. *Id.* at 581:19. Then, because opposites attract, the protein will migrate to the positive electric charge. *Id.* at 581:21-22. The protein's migration is impeded by an acrylamide gel that is

applied to the apparatus. *Id.* at 581:22-24. One can determine the size of the protein based upon the speed at which it travels through the gel. Thus, "[t]hings that are small move faster and things that are big move slower." *Id.* at 581:24 to 582:1. Because the apparatus contains a number of lanes or wells, different substances can be placed side-by-side for comparison. When compared with known standards, a substance's molecular weight can be approximated. *Id.* at 583:8-15. Substances with low molecular weights move quickly while those with high molecular weights migrate slowly through the gel. One can also identify the relative size of the protein's glycosylation by using SDS-PAGE. *Id.* at 592:14-20. The experimenter can compare a glycosylated protein with the same type of protein that has been treated so as to cause deglycosylation. *See id.* at 582:811. As one might expect, a deglycosylated protein migrates farther on SDS-PAGE than the glycosylated protein because the latter is weighed down by its attached sugar chains. The difference between the distances that these proteins migrate through the acrylamide gel represents the apparent molecular weight of the glycosylation of that protein. *Id.* at 590:16-22, 592:14-20.

The experimenter can analyze the data provided by the SDS-PAGE test by employing the Western blot. First, the researcher takes the SDS-PAGE gel and attaches it onto a piece of paper called nitrocellulose. *Id.* at 582:19-20. After the nitrocellulose and acrylamide come together, an electric field is run horizontally through the gel, which transfers the proteins from the gel to the paper. *Id.* at 582:20-24. The paper has both molecular weight markers stained with color that act as standards and different proteins. *Id.* at 582:25 to 583:1. The nitrocellulose can then be stained with an antibody to identify a desired protein. *Id.* at 583:2-3. Once identified, the relevant protein's migration can be compared with the migration of the known standards, yielding a molecular weight approximation. *See id.* at 583:4-6, 19-23; 590:24 to 591:9. More precisely, one can observe differences in the

distances each substance migrates on the nitrocellulose. This technique is known as Western blotting.

Another technique employed by those skilled in the art in 1983 was isolectric focusing ("IEF"). IEF resembles SDS-PAGE except that sodium dedecyl sulfate is not introduced to the protein to provide a negative charge to the sample. *See id.* at 588:5-23. Instead, in an IEF experiment, the protein's inherent charge moves the protein top to bottom through the gel which contains a pH gradient. *Id.* at 588:8-13, 589:13-16. Varying types of sugars have varying charges, so for example, all other things being equal, proteins that have a large number of sialic acids are more negatively charged than proteins that have fewer sialic acids. *See id.* at 605:9-16. The protein migrates until its inherent charges are neutralized by the pH gradient. *Id.* at 588:13-15, 605:13-16. "So in general if you had a collection . . . of erythropoietin glycoproteins differing in sialylation, one could distinguish the different glycoforms by IEF gel . . . ." *Id.* at 605:24 to 606:2. Similarly, by employing IEF, a researcher can separate and identify proteins on the basis of their charge. *Id.* at 588:18-23.

Dr. Cummings also explained that the patent disclosed Amgen's use of these techniques in order to show glycosylation differences between its recombinant EPO glycoproteins and the naturally occurring prior art urinary EPO glycoproteins. *See id.* at 614:9-25; Trial Ex. 1 at 28:33-50. As disclosed in Column 28 of the patent, these studies revealed that according to Western blot and SDS-PAGE analyses, "the CHO-produced EPO material had a somewhat higher molecular weight than the COS-1 expression product which, in turn, was slightly larger than the pooled source human urinary extract." Trial Ex. 1 at 28:38-41. Amgen scientists then treated the proteins with neuraminidase, which removes the sialic acids from the protein. *Id.* at 28:42-43; Trial Tr. at 611:17-18. Following neuraminidase treatment, the COS-1 and CHO recombinant products had approximately equal

apparent molecular weights, but were both nonetheless larger than the resulting asialo human urinary extract. *See* Trial Ex. 1 at 28:42-46; Trial Tr. at 613:1-11. Amgen then treated the CHO and human urinary products with endoglycosidase F, which removes not only sialic acids, but also any other carbohydrate chains attached to the protein. Trial Ex. 1 at 28:46-48. Amgen scientists discovered that the CHO and urinary products were "substantially homogenous products having essentially identical molecular weight characteristics." *Id.* at 28:49-50; Trial Tr. At 613:12-17. The conclusion to be drawn from this series of tests is that the difference in the apparent molecular weights of recombinant and urinary EPO products on SDS-PAGE and Western blot is explained by differences in glycosylation between the two types of EPO glycoproteins. Trial Tr. at 613:23 to 614:1. ("[T]he results then demonstrate the difference in mobility of these proteins compared to the urinary derived EPO is due to a difference in asparagine glycosylation and due to a difference in sialic acid content."). In light of this data reported in Column 28, one skilled in the art in 1983 would understand that "the recombinant proteins are glycosylated differently than the naturally-occurring protein, and that these differences can be revealed by running an SDS-PAGE and doing a western blot as described here." *Id.* at 620:1-5.

In the final paragraph of Column 28, Amgen disclosed the results of another set of experiments intended to show differences in glycosylation between recombinant and urinary EPO products. Trial Ex. 1 at 28:51-67. Amgen performed "carbohydrate analyses" in order to identify the individual monosaccharide sugar residues present on both the EPO derived from CHO cells and derived from urine. *See id.*; Trial Tr. at 620:20-23.

> [I]n this experiment the glycoprotein is taken and hydrolyzed in the presence of acid . . . and that cleaves the bonds between the amino acids, cleaves the bonds

> between the individual sugar residues. . . . [A]ll the sugars then are present unlinked to each other as individual monosaccharides. They can be labeled and separated by some chromatographic method. So that, say the sialic acids are separated from the N-acetylglucosamines and Fucose and so forth.

Trial Tr. at 621:15-24. Once all of the sugars are separated and identified, their relative distribution can be calculated. *Id.* at 621:24 to 622:1. In particular, one type of sugar is designated as one, and the other sugars are compared by their abundance in relation to the standardized sugar. *Id.* at 622:1-5. In the nomenclature of the patent specification, one can identify the carbohydrate constitution values expressed as molar ratios of the carbohydrates in the product. Trial Ex. 1 at 28:56-58. Using this method, the patent reveals that the recombinant EPO product contains a higher ratio of N-acetylneuraminic acid (.998) than the urinary EPO product (.930).[36] *Id.* at 28:56-66. This difference in the carbohydrate constitution values between the recombinant and urinary EPO glycoproteins is "consistent with the Western blot and SDS-PAGE analysis described above." *Id.* at 28:66-67.

Dr. Cummings also conducted experiments in order to determine whether there are glycosylation differences between TKT's product and urinary EPO. Trial Tr. at 629:18-

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[36] The patent also reports an erroneous Hexose value for the CHO derived EPO product (15.09) compared to the urinary derived EPO product (1.73). Trial Ex. 1 at 28:56-66. Dr. Cummings explained that "it would be obvious to anybody else in the field who looks at these values" that the recombinant product's Hexose value was erroneous because neither he nor anybody else that he knew had ever seen such high Hexose content in a glycoprotein. Trial Tr. at 623:5-9, 17-19. Apparently, because sugars are prevalent—our clothes are made of glucose which is a Hexose—contamination of the carbohydrate analysis can occur. *Id.* at 623:11-16. Dr. Cummings suspected that such contamination explained the high Hexose values reported in the patent specification. *Id.* at 623:16-19.

23. He concluded that "the recombinant erythropoietin made by TKT is clearly different in glycosylation from the naturally occurring erythropoietin in human urine." *Id.* at 629:18-20. Specifically, Dr. Cummings performed both SDS-PAGE and Western blot analyses and IEF experiments to compare the products. *See id.* at 629:25 to 630:9, 648:19-21.

His SDS-PAGE and Western blot analyses indicate that HMR4396 has a higher apparent molecular weight than the naturally occurring EPO and that the difference is due to differences in glycosylation. *Id.* at 630:5-9. Following the techniques described in the Amgen patent specification, Dr. Cummings ran the SDS-PAGE gels both prior to and after deglycosylation treatment with sialidase and endoglycosidase. *See id.* at 631:8-15. After deglycosylation, the mobility of the compared proteins was substantially similar, raising the inference that differences in migration on the initial gel were due to differences in glycosylation. *Id.* at 631:13-21. Dr. Cummings repeated the experiments and obtained similar results leading to the same conclusion: TKT's EPO product has glycosylation which differs from that of human urinary EPO. *See id.* at 645:17 to 648:20.

In conducting IEF experiments, Dr. Cummings compared HMR4396 with urinary EPO. *Id.* at 649:11-14. The urinary EPO traveled farther down the gel than the recombinant EPO indicating that the urinary EPO is more acidic than HMR4396's EPO. *Id.* at 649:15-17. Dr. Cummings concluded that these results were consistent with the SDS-PAGE results indicating that TKT's recombinant EPO is glycosylated differently (probably due to the sialic acids) than urinary EPO. *Id.* at 649:17-21.

If left undisturbed by effective cross-examination or credible contradictory evidence, Dr. Cummings' testimony regarding his experiments would discharge Amgen's duty of showing by a preponderance of the evidence that HMR4396 has glycosylation which differs from that of human urinary

EPO. In such a scenario, a finding of literal infringement as to this claim limitation in the '933 patent would follow. TKT, however, made great headway on these matters and, in the end, cast so much doubt upon Amgen's proof that a finding of no literal infringement is warranted.

Though ultimately deemed unpersuasive, TKT first argued that the SDS-PAGE experiments its expert conducted, which compared GA-EPO with urinary EPO samples, revealed no difference in glycosylation because there was no detectable difference between the migration of GA-EPO and two of the urinary EPO samples. *See* Trial Exs. 138, 139, 2012, 2451, 2452; Trial Tr. at 2319:10 to 2321:5, 2340:20-23; Strickland Designated Dep. (Sept. 14, 1999) at 288-356. In particular, TKT compared GA-EPO samples with urinary EPO samples prepared by Dr. Tom Strickland following the Miyake procedure referenced in the patent. *See* Trial Exs. 138, 139, 2012; Strickland Designated Dep. (Sept. 14, 1999) at 288 356. TKT compared GA-EPO to two urinary EPO samples (uEPO2 and uEPO3) purified from the 17 mM DEAE-agarose fraction and a urinary EPO sample (uEPO1) purified from the 30 mM DEAE-agarose fraction. Trial Tr. at 2316:10 to 2319:9, 2343:5-15. TKT contends that because there was no detectable difference between the migration of GA-EPO and the uEPO2 and uEPO3 urinary EPO samples, their glycosylation must be identical.

TKT's contention fails as a matter of logic. The fact that Dr. Strickland's experiments reveal that the GA-EPO and two urinary EPO samples migrated an equal distance does not imply that their *glycosylation* is the same. Rather, one can infer only from this that the apparent molecular weights of these glycoproteins is the same. *See id.* at 581:21-24. In order to make the additional inference that the two proteins have the same glycosylation, one must first treat the glycoproteins with enzymes that cause deglycosylation, and then these deglycosylated products must be run through the SDS-PAGE

gel and compared. *See id.* at 582:8-11, 592:14-20. If the *deglycosylated* products travel down the gel the same distance (implying an equivalent apparent molecular weight), only then one can infer that the fact that the GA-EPO and two urinary EPO samples migrated an equal distance was not due to a difference in glycosylation. TKT failed to do this latter step, making Strickland's experiment inconclusive as to whether the glycosylation of the GA-EPO and urinary EPO differs. Thus, the Court finds TKT's SDS-PAGE experiments involving GA-EPO and uEPO unpersuasive in rebutting Amgen's prima facie showing through Dr. Cummings of glycosylation differences between GA-EPO and urinary EPO.

TKT's second tack, however, leads it through the breakers and into a safe harbor. In short, TKT's evidence shows that different urinary EPO samples can themselves have glycosylation differences depending on how they are purified. As a result, Dr. Cummings' evidence that GA-EPO differs from one type of urinary EPO is insufficient as matter of fact to prove literal infringement.

Returning to the claim language, as construed by the Court, "human urinary erythropoietin" contains no limitation as to the source, purity, or method of preparation of the EPO other than that it be "derived from human urine." Tr. of *Markman* Hr'g, Vol. III at 112; Trial Tr. at 702:9 to 703:18, 1843:1-11; *supra* Section II.J, at 42-44. The claim language also provides no guidance regarding levels of EPO yield in or biological activity of the urinary EPO preparation. Trial Tr. at 703:19 to 704:7. Moreover, although the patent specification refers to different urinary EPO preparations and methods for purifying urinary EPO, including the methods of Miyake et al. and Yanagawa et al., Trial Ex. 1 at 7:3-23, 8:9-15; Trial Tr. at 633:5-21, 1978:12 to 1979:6, 2731:12-14, in the portion of the patent specification describing glycosylation experiments with recombinant and urinary EPO products, no specific information is provided regarding how to select a urinary

EPO preparation for purposes of comparison, *see* Trial Ex. 1 at 28:33-50. Furthermore, the patent does not specify which urinary EPO preparation ought be used as a standard in determining whether a particular EPO sample has glycosylation which differs from that of human urinary EPO. Trial Tr. at 786:6 to 787:11, 1846:23-25, 1978:12 to 1980:1, 1981:20 to 1982:1. Though a skilled worker might be able to guess, such an artisan reading the '933 patent would not know which urinary erythropoietin preparation should be used as a standard in making the comparison described in the patent and called for by the claims. *See id.* at 1981:20 to 1982:7.

This lack of direction regarding the selection of a urinary EPO standard is important because different urinary EPO preparations have different glycosylation due to the action of "glycosyltransferases," which are enzymes that add carbohydrate structures to the EPO molecule, *see id.* at 575:12 to 577:15, 1847:13 to 1848:5. The EPO molecule contains four carbohydrate chains attached at specific amino acids on the protein. Denoted by asterisks in Figure 6 of the patent, three of these four chains are "N-linked" chains and are linked to the amino acid arginine at positions 24, 38, and 83 of the EPO-molecule, while the fourth chain is an "O-linked" chain and is linked to the amino acid serine at position 126. *Id.* at 1962:22 to 1963:6. As explained in greater detail during trial, the heterogeneity of EPO glycosylation is manifested by differences in the number, type, and arrangement of the individual monosaccharides that make up the carbohydrate chains. *See id.* at 606:4-20, 759:19 to 767:18, 1847:13 to 1849:22, 1964:3 to 1966:10. For example, all other things being equal, an EPO preparation consisting of EPO molecules that have a higher number of tetra-antennary structures would migrate differently on SDS-PAGE from an EPO preparation consisting of EPO molecules that have a higher number of triantennary carbohydrate structures. *Id.* at 763:14 to 764:1.

In addition, the use of different methods of purifying erythropoietin results in different glycosylated erythropoietin

populations. TKT submitted evidence indicating, for instance, that after undergoing ion exchange column chromatography, one sample of EPO separates into different glycosylated populations. *Id.* at 1966:14 to 1968:2, 2136:9-16, 2161:25 to 2162:13; Strickland Designated Dep. (Feb. 8, 2000) at 71:5 to 72:10. In fact, another of Amgen's patents describes the separation of EPO molecules that differ from each other by as few as one sialic acid using ion exchange column chromatography. *See* Trial Ex. 2130 at 14:57 to 15:4. In 1984, there were several other purification methods available to ordinary skilled workers. *See* Trial Exs. 42, 2012, 2233, 2235-36, 2247, 2252, 2333, 2440; Trial Tr. at 632:13 to 634:1, 1846:19-22, 1970:6 to 1979:8, 2189:16 to 2190:25, 2193:9 to 2194:15, 2197:2-19. The 1977 Miyake et al. publication, for example, describes the purification from the same starting material of two homogeneous urinary EPO preparations (Fraction II and Fraction IIIA) that had about the same potency in terms of biological activity. *See* Trial Ex. 2012 at 5558, 5562-63. Fractions II and IIIA, later known as α and β urinary EPO, Trial Ex. 2439 at 2294; Trial Tr. at 772:25 to 773:5, 1972:2-6, had different carbohydrate compositions and, therefore, differed from each other in glycosylation, *see* Trial Ex. 2023 at A45537; Trial Ex. 2439 at A25197; Trial Tr. 1972:816. Thus, these two uEPO preparations, though produced by the same procedure (Miyake) and derived from the same batch of material, nonetheless had different glycosylation.

Additional experiments conducted by Amgen scientists in 1984 showed that different urinary EPO preparations had different glycosylation. In the spring of 1984, in conjunction with scientists from Kirin, Dr. Strickland purified EPO from the urine of a single patient using a modified Miyake procedure. *See* Trial Ex. 2013 at A 90211-48; Trial Ex. 2400 at A 95587; Strickland Dep. (Sept. 13, 1999) at 86:13 to 88:23, 91:5-10. This urinary EPO was referred to as "Lot 82" urinary EPO. Strickland Designated Dep. (Sept. 13, 1999) at

88:2-12, 91:5-10. Dr. Joan Egrie conducted a series of SDS-PAGE experiments comparing Lot 82 EPO with a uEPO received from Dr. Eugene Goldwasser.[37] Dr. Egrie compared the preparations side-by-side on the same gel and concluded that the Lot 82 and Goldwasser uEPO samples migrated differently on SDS-PAGE, with the Lot 82 material having a higher molecular weight. *See* Trial Ex. 126 at A4719-23, A4724-25, A4743-49, A4758-65, A4788-93; Trial Ex. 2400 at A95587-98; Trial Ex. 2094 at A4913-21; Trial Tr. at 2287:6 to 2291:15. After performing additional tests before and after treatment with enzymes effecting deglycosylation, she also concluded that this difference in migration was due to differences in glycosylation. In particular, the Lot 82 and Goldwasser uEPO migrated differently before enzymatic treatment, and the two preparations migrated the same after such treatment. These tests confirmed that the difference in apparent molecular weight between Lot 82 and Goldwasser uEPO was caused by differences in glycosylation. *See* Trial Ex. 126 at A4558-65; Trial Ex. 2400 at A95587, A9559091, A95593-98; Trial Tr. at 2290:1 to 2293:9. Dr. Egrie came to the same conclusion when she compared a commercially available urinary EPO from Alpha-Therapeutics to Goldwasser uEPO. *See* Trial Ex. 126 at A4788-93; Trial Ex. 2400 at A95590-91. Moreover, Dr. Egrie's various SDS-PAGE experiments reveal that different uEPOs have varying glycosylation. Trial Tr. at 2289:13 to 2294:9, 2294:22 to 2295:5. In light of this evidence, a skilled artisan in 1984 would have understood that urinary erythropoietin samples obtained using different purification methods could have different glycosylation. *id.* at 1846:12-25, 1966:14 to 1967:1, 1970:10-25, 2303:9-17; *see also* Browne Designated Dep. (Sept. 17, 1999)

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[37] Though Dr. Cummings criticized Dr. Egrie's methodology in these experiments, the Court finds that the use of iodinated samples did not affect the results she obtained. Trial Tr. 807:25 to 808:9, 2293:10 to 2295:25.

at 226:3 to 227:19. As a result, the glycosylation of human urinary erythropoietin was in 1984, and continues to be, a moving target.

The claim language of the '933 patent, however, presupposes that the glycosylation of urinary erythropoietin is a fixed, identifiable marker against which the glycosylation of recombinant EPOS can be measured. Yet, how can one prove that a recombinant EPO has glycosylation which differs from that of urinary EPO when the glycosylation of urinary EPO itself varies? The Court need not answer this conundrum. All that need be said is that Amgen's showing that GA-EPO has glycosylation which differs from but one of the many heterogeneous urinary EPOs is insufficient to carry its burden of proving by a preponderance of the evidence that TKT infringes this claim limitation. Consequently, the Court finds that HMR4396 does not literally infringe Claim 1 of the '933 patent.

Claim 2 is dependent upon Claim 1 and differs only in that the glycoprotein product's molecular weight, as measured by SDS-PAGE, must be higher than that of human urinary EPO. Trial Ex. 2 at 38:22-25. Because of its dependency upon non-infringed Claim 1, the Court finds no literal infringement of Claim 2. In addition, the Court finds that Amgen's evidence that the GA-EPO has a higher molecular weight than urinary EPO suffers from the same deficiency as its proof regarding their differences in glycosylation because the molecular weights of uEPOs vary as well.[38] A finding of literal non-

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[38] Amgen's Dr. Strickland attempted to purify human urinary EPO using the Miyake method. *See* Trial Exs. 138, 139; Trial Tr. at 2310:20 to 2311:4; Strickland Designated Dep. (Sept. 14, 1999) at 288-356. Dr. Strickland discovered that the EPO separated into two different fractions—a 17 mM fraction and a 30 mM fraction—from which he collected uEPO. *See* Trial Ex. 139 at AM 77 000101, AM 77 000138-42, AM 77 000152-53; Trial Ex. 2461; Trial Tr. at 2311:7 to 2312:1, 2343:5-15. Dr. Strickland separately purified EPO from each fraction and subjected the

infringement of Claim 2 of the '933 patent therefore follows.

Claim 9 recites a "pharmaceutical composition comprising an effective amount [of] a glycoprotein product effective for erythropoietin therapy according to Claim 1, 2, 3, 4, 5, or 6 and a pharmaceutically acceptable diluent, adjuvant or carrier." Trial Ex. 2 at 39:1-4. Because, in this litigation, Claim 9 is dependent upon either Claim 1 or Claim 2 and the Court has found that GA-EPO literally infringes neither, so too with respect to Claim 9.[39] Thus, because Amgen's proof on the limitation requiring the erythropoietin glycoprotein to have glycosylation which differs from that of human urinary erythropoietin was insufficient, the Court finds that all three

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EPO obtained therefrom to SDS-PAGE. *See* Trial Ex. 139 at AM 77 000138-42, AM 77 000152-53; Trial Ex. 2012 at 5563; Trial Ex. 2316 at AM 77 000271-72; Trial Tr. at 2317:15 to 2318:19. These SDS-PAGE experiments revealed that the EPO obtained from the 17 mM fraction migrated more slowly than that of the 30 mM fraction, thus indicating the 17mM fraction's higher apparent molecular weight. *See* Trial Ex. 139 at AM 77 000152-53; Trial Ex. 2316 at AM 77 000271-76; Trial Tr. at 2312:2 to 2314:2; Strickland Designated Dep. (Feb. 8, 2000) at 57:24 to 63:6; Strickland Designated Dep. (Sept. 14, 1999) at 352:6 to 353:8. TKT also compared the 17 mM and 30 mM urinary EPO fractions on SDS-PAGE and found that two 17 mM fractions (identified as uEPO2 and uEPO3) migrated more slowly than the 30 mM purified sample (uEPO1). *See* Trial Ex. 2447 at HMR806130; 2449-52; Trial Tr. at 2343:5 to 2344:21, 2351:14 to 2352:10.

[39] But for its dependency upon non-infringed claims, judgment of infringement on Claim 9 would be appropriate in light of the evidence regarding the other limitations in Claim 9. HMR4396 Injection is a pharmaceutical composition. *See* Trial Ex. 18 at IND000019; Trial Ex. 27 at IND501303-04; Hancock Designated Dep. at 242:9 to 243:25, 282:8-21. It also contains an amount of a glycoprotein product effective for erythropoietin therapy. *See* Tr. of *Markman* Hr'g, Vol. II at 135:25 to 136:2. Finally, HMR4396 Injection contains a phosphate buffer, which is a pharmaceutically acceptable diluent. *See* Tr. of Summ. J. Hr'g (Apr. 26, 2000) at 65; Hancock Designated Dep. at 242:22 to 243:11.

of the asserted claims of the '933 patent are not literally infringed.

Amgen's evidence is also insufficient to show infringement under the doctrine of equivalents. Amgen points to evidence submitted during trial that tends to show that HMR4396 is nothing more than a "me too" product. Trial Tr. 2231:9-10 (defining "me too" product as "one that simply copies an existing product"). Documentary and testimonial evidence indicates that the goal of the HMR4396 project was to make a product therapeutically equivalent, rather than superior, to Amgen's EPOGEN®. *See* Trial Ex. 160 at HMR 007088; Trial Ex. 162 at HMR 017347; Trial Ex. 16S at HMR 028663; Trial Ex. 166 at TKT 005008; Trial Ex. 170 at HMR 346024-26; Trial Ex. 173; Trial Ex. 180 at HMR 305229; Trial Ex. 196 at HMR 042121; Trial Tr. at 2224:10-22, 2229:18 to 2230:11, 2230:22 to 2233:22, 2236:19 to 2240:2; Hancock Designated Dep. at 206:22 to 209:23; Fike Designated Dep. at 65:15-20. Moreover, it appears that TKT achieved nothing more than equivalence: TKT admitted to the FDA that its clinical trials show that HMR4396 and EPOGEN® are equivalent in their clinical properties, and that patients given HMR4396 had more negative reactions than those given EPOGEN®. *See* Trial Ex. 122 at HMR 801225, 801229, 801231, 801233, 801281-83; Trial Ex. 123 at HMR 801510; Trial Tr. at 492:8 to 493:1, 556:25 to 557:9, 1949:2 to 1953:2; Hahner Designated Dep. at 348:14 to 350:7, 351:20 to 352:20, 410:8 to 411:15, 444:16 to 447:18; Hancock Designated Dep. at 251:25 to 253:10. Thus, the Court finds that HMR4396 has no demonstrable advantages over EPOGEN®. *See* Trial Ex. 159 at HMR 005237; Trial Ex. 177 at HMR 413257; Trial Tr. at 2229:15 to 2230:11; Hahner Designated Dep. at 265:2-6; Treco Designated Dep. at 663:23 to 664:17.

However, this general finding is insufficient to establish infringement under the doctrine of equivalents. A claim limi-

tation is equivalently present in an accused product if there are only "insubstantial differences" between the limitation and the corresponding aspects of the product. *CAE Screenplates Inc.* v. *Heinrich Fiedler GMBH & Co.*, 224 F.3d 1308, 1319 (Fed. Cir. 2000). "The usual test of the substantiality of the differences is whether the element in the accused composition performs substantially the same function in substantially the same way to obtain substantially the same result as the claimed element." *Upjohn Co.* v. *Mova Pharm. Co.*, 225 F.3d 1306, 1309 (Fed. Cir. 2000); *see also Graver Tank Mfg. Co.* v. *Linde Air Prods. Co.*, 339 U.S. 605, 608 (1950). The Supreme Court has recently explained in *Warner-Jenkinson Co.* v. *Hilton Davis Chemical Co.*, 520 U.S. 17 (1997), that the doctrine of equivalents is limited, however, so that "[e]ach element contained in a patent claim is deemed material to defining the scope of the patented invention, and thus the doctrine of equivalents must be applied to individual elements of the claim, not to the invention as a whole." *Id.* at 29. Thus, in order to show infringement under the doctrine of equivalents, one must prove not only that the accused product is *generally* equivalent to the patented product, but also that a *specific element* of the accused product is substantially equivalent to that *same element* of the patented product.

The Court finds that Amgen's evidence regarding general therapeutic similarities between HMR4396 and EPOGEN® fails to meet the Supreme Court's requirement that plaintiffs asserting the doctrine of equivalents must produce evidence with respect "to individual elements of the claim, not to the invention as a whole." *Warner-Jenkinson,* 520 U.S. at 29. None of this evidence persuades the Court of the precise—and more salient—point that the claim term requiring glycosylation which differs from that of human urinary erythropoietin is met equivalently by HMR4396. Accordingly, it is insufficient to ground Amgen's claim under the doctrine of equivalents.

Amgen did, however, present some evidence that moved closer to the specificity required by the Supreme Court. In particular, Amgen presented evidence that any glycosylation pattern differences between HMR4396 and EPOGEN® are relatively insubstantial. *See* Trial Ex. 168 at HMR 102737; Trial Ex. 171 at HMR 314992; Trial Ex. 173 at TKT 006145; Trial Ex. 182 at L002293; Trial Ex. 183 at L001918; Trial Ex. 197 at HMR 472507; Trial Tr. at 2245:22 to 2252:23. Amgen's theory is thus: if the glycosylation of EPOGEN® differs from that of human urinary erythropoietin and glycosylation differences between HMR4396 and EPOGEN® are relatively insubstantial, then the glycosylation of HMR4396 must similarly differ from that of human urinary erythropoietin. The theory itself is quite tenuous, and the proof of it unpersuasive. Because Amgen failed both to establish the necessary facts by a preponderance of the evidence and to tie these inferences together in a persuasive manner, the Court finds that it failed to shoulder its burden of proof. Despite Amgen's rapid bailing, the doctrine of equivalents does not rescue its sinking infringement ship. Consequently, the Court determines that the '933 patent is not infringed.

3. *The '080 Patent*

The asserted independent claims of the '080 patent pertain to erythropoietin glycoproteins that (1) have the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells; (2) comprise the mature erythropoietin amino acid sequence of Figure 6; and (3) are either non-naturally occurring (Claim 2) or isolated but not from human urine (Claim 3). Trial Ex. 3 at 38:32-50. Dependent Claim 4 lays claim to a pharmaceutical composition comprising a therapeutically effective amount of the glycoprotein product according to Claims 2 or 3. *Id.* at 38:51-53. As previously explained, the Court found at the close of Amgen's infringement case that the '080 patent was not literally infringed. *See supra* Section IV.C.1, at 61-66.

Though defeated in the engagement over literal infringement, Amgen has not retreated from the infringement battlefield. Instead, it sails on under the doctrine of equivalents. In analyzing whether each and every limitation of the claim is literally or equivalently present, *CAE Screenplates Inc.*, 224 F.3d at 1318-19, the Court first addresses those claim terms that are literally present in HMR4396.

The Court has previously held or it is undisputed that HMR4396 (1) is an "erythropoietin glycoprotein," Joint Pretrial Mem. at 5, ¶ 27; Tr. of *Markman* Hr'g, Vol. II at 134:12-16, 136:13-14; (2) has "the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells," Joint Pretrial Mem. at 5, ¶ 24; Tr. of *Markman* Hr'g, Vol. II at 134:17-20, 136:15-16; *see also supra* Section IV.E.2, 127-28; (3) is not isolated from human urine, Trial Ex. 19 at 506, 547 (IND for HMR4396); *see also* Am. Answer ¶ 25 (admitting that GA-EPO is not isolated from human urine); (4) is a "non-naturally occurring" erythropoietin glycoprotein, *see supra* Section IV.E.2, at 125-27; and (5) with respect to the additional limitations contained in dependent Claim 4, HMR4396 Injection is a "pharmaceutical composition" comprising a "therapeutically effective amount [of] an erythropoietin glycoprotein product," Joint Pretrial Mem. at 5, ¶ 26; Tr. of *Markman* Hr'g, Vol. II at 130:17-20, 136:13-14; *see also supra* Sections III.A, III.B.

Claim 2 of the '080 patent claims an "isolated" erythropoietin glycoprotein having certain additional characteristics. Trial Ex. 3 at 38:39. Although the Court did not construe the term "isolated" during the *Markman* hearing, the term's meaning can be inferred from its use in the specification. For example, the patent refers to "[i]nitial attempts to isolate erythropoietin from urine," Trial Ex. 1 at 7:3, and it later states that "[o]ther isolation techniques utilized to obtain purified erythropoietin involve immunological procedures."

Id. at 7:43-44; *see also id.* at 11:15-19. After considering these excerpts from the patent, Dr. Lodish testified that one of ordinary skill in the art would understand the term "isolate" to mean "to recover in pure form." Trial Tr. at 193:4 to 194:3. The Court agrees. The Court also agrees with Dr. Lodish that HMR4396 is isolated as that term is used in the patent. *Id.* at 211:22 to 212:2. The IND for HMR4396 identifies a combination of column chromatography and ultrafiltration steps to recover erythropoietin in pure form from its cultured cells. *See* Trial Ex. 19 at IND000506. Thus, Amgen has proven by a preponderance of the evidence that HMR4396 literally meets the requirement of Claim 2 that the erythropoietin glycoprotein be "isolated."

Thus, the Court finds as matter of fact that all the limitations in the asserted claims of the '080 patent are literally infringed by HMR4396 or HMR4396 Injection except for the limitation that the erythropoietin glycoprotein comprise "the mature erythropoietin amino acid sequence of FIG. 6," Trial Ex. 3 at 38:36, 38:43, 38:48-49. The Court found previously that because TKT's cells produce an erythropoietin glycoprotein comprising a 165 amino acid sequence rather than the 166 amino acid sequence depicted in Figure 6, HMR4396 did not literally infringe the asserted claims of the '080 patent. *See supra* Section IV.C.1, at 61-66. Amgen contends, however, that this claim limitation is infringed under the doctrine of equivalents. As a result, the question boils down to whether, despite having a 165 amino acid sequence, HMR4396 performs substantially the same function in substantially the same way to obtain substantially the same result as an erythropoietin glycoprotein containing 166 amino acids. The Court finds that it does and, consequently, concludes that HMR4396 infringes the '080 patent under the doctrine of equivalents.

The question focuses narrowly on the effect of the arginine at the 166 position of Figure 6. The 165 amino acid EPO

sequence of HMR4396 is identical to amino acids 1 through 165 in Figure 6. *See* Trial Ex. 18 at IND000019; Trial Ex. 23 at IND002191; Trial Ex. 25 at IND002357; Trial Ex. 29 at IND002470, 002480; Trial Ex. 2299 at L7828; Trial Tr. at 175:19-25, 199:15 to 211:13, 213:210. Likewise, the glycosylation sites of HMR4396 are identical to those depicted in Figure 6. *See* Trial Ex. 25 at IND002357; Trial Tr. at 202:17-20. As a result, the only difference between the amino acid sequence of HMR4396 and that of Figure 6 is the additional amino acid, arginine, at position 166, or at the "C-terminus," of Figure 6.

The Court finds that Amgen has shown by a preponderance of the evidence that the presence or lack of this arginine at the C-terminus of these glycoproteins does not make them materially different. An erythropoietin glycoprotein containing either amino acid sequence has the same conformational structure and biological activity. Importantly, the Court finds that the lack of the arginine residue at the C-terminus does not affect the *in vivo* biological activity of the EPO product. To prove this point, Amgen presented evidence regarding a study comparing erythropoietin lacking four amino acids normally found at the C-terminus (163-166) and the normal protein, referred to in the study as "wild-type." *See* Trial Ex. 54 at IND000181. Employing biological assays, the researchers discovered that such changes at the C-terminus neither affect the biological activity of the protein nor inhibit proper secretion from the cells. *See id.*; Trial Tr. 214:6-22, 215:21 to 216:20. The clear inference from this evidence is that if the glycoprotein is substantially the same when its last four amino acids are removed, then the absence of but one of these four should not cause any significant differences. Trial Tr. at 214:20-22. The Court accepts this inference and is persuaded by it.

In reaching his conclusion that the arginine does not materially affect the erythropoietin glycoprotein, Dr. Lodish

relied upon an article that identified the portions of the erythropoietin protein that are important for binding to the EPO receptor. *See id.* at 218:9 to 219:10. According to Dr. Lodish, the paper concludes that the C-terminus does not form part of the binding site. *Id.* at 219:1-3. As a result, one of ordinary skill in the art "would expect small changes at the C terminus would have no effect on the binding property." *Id.* at 219:4-5. Similarly, Dr. Lodish relied upon experiments performed at Amgen that, according to him, showed that an erythropoietin glycoprotein containing an arginine residue at position 166 functions in the same way to achieve the same result as an erythropoietin glycoprotein lacking the arginine. *See id.* at 219:11 to 220:2, 223:10-11. The Court credits Dr. Lodish's testimony on these matters.

TKT attempted to whittle away at Amgen's evidence on equivalence. On cross-examination, Dr. Lodish admitted that a change in the amino acid sequence of a protein can in many cases have adverse immunological effects in the clinical use of that protein. *See id.* at 501:12-21. TKT also elicited testimony from Dr. Kingston explaining that a change in even just one amino acid can have a significant effect on the clinical function of a protein. *Id.* at 1245:22 to 1246:3. While these general statements may be true, they are ineffective in rebutting Amgen's more precise evidence specifically tailored to slight variations in the amino acid sequence of erythropoietin. Similarly, TKT's evidence comparing GA-EPO to Amgen's EPOGEN® is either irrelevant or too speculative to warrant the Court to find that GA-EPO is significantly different from EPOGEN®, and more importantly, that any such difference is due to GA-EPO's absence of the arginine at position 166. *See* Trial Ex. 122 at HMR 801231; Trial Tr. at 2225:15 to 2227:17.

Thus, the Court finds that Amgen has proven by a preponderance of the evidence that, despite lacking the arginine at position 166, HMR4396 performs substantially the same

function in substantially the same way to obtain substantially the same result as an erythropoietin glycoprotein containing 166 amino acids. Consequently, Amgen has proved that HMR4396 meets each of the limitations of the asserted claims of the '080 patent either literally or by equivalence.

In order to reach this conclusion, the Court necessarily rejects TKT's contention that prosecution history estoppel precludes Amgen's reliance on the doctrine of equivalents. TKT argues that during the prosecution of the '080 patent, Amgen added the limitation "the mature erythropoietin amino acid sequence of FIG. 6" to distinguish its glycoprotein claims from those of the already issued '933 patent, which were not limited by a precise amino acid sequence. In particular, following an interview with Examiner Martinell in December of 1996, *see* Trial Ex. 3 Tab 4, Amgen amended the pending claims to limit the glycoprotein claimed to one having the mature erythropoietin amino acid sequence of Figure 6, *see* Trial Ex. 3 Tab 6 at 162. In submitting these amendments, Amgen specifically told the Patent Office that the added limitation distinguished its pending '080 claims from those of the '933 patent: "Applicant notes that claims 69, 70 and 71[, corresponding to issued Claims 1, 2, and 3 of the '080 patent,] all differ in scope from glycoprotein claim 1 of U.S. 5,547,933 in specifying that the claimed subject matter comprises the mature human erythropoietin sequence of Figure 6." *Id.* at 164.

The Court finds, however, that estoppel is inappropriate in this circumstance because Amgen did not add this claim limitation in an attempt to overcome a rejection, to avoid prior art, *see Warner-Jenkinson Co.* v. *Hilton Davis Chem. Co.*, 520 U.S. 17, 3031 (1997), or indeed for any reason related to the statutory requirements for a patent. *See Festo Corp.* v. *Shoketso Kinzoku Kogyo Kabushiki Co., Ltd.*, No. 95-1066, 2000 WL 1753646, at *6 (Fed. Cir. Nov. 29, 2000) (noting that prosecution history estoppel is not limited to

avoiding prior art but includes any reason that relates to the statutory requirements of a patent). The limits of the doctrine of prosecution history estoppel were recently explained by the Supreme Court. In *Warner-Jenkinson*, the petitioner, not unlike TKT here, sought to extend the theory such that "any surrender of subject matter during patent prosecution, regardless of the reason for such surrender, precludes recapturing any part of that subject matter, even if it is equivalent to the matter expressly claimed." 520 U.S. at 30. The Supreme Court responded:

> But petitioner reaches too far in arguing that the reason for an amendment during patent prosecution is irrelevant to any subsequent estoppel. In each of our cases cited by petitioner and by the dissent below, prosecution history estoppel was tied to amendments made to avoid the prior art, or otherwise to address a specific concern—such as obviousness—that arguably would have rendered the claimed subject matter unpatentable.

Id. at 30-31. After quickly reviewing a handful of its estoppel cases, the Supreme Court continued:

> It is telling that in each case this Court probed the reasoning behind the Patent Office's insistence upon a change in the claims. In each instance, a change was demanded because the claim as otherwise written was viewed as not describing a patentable invention at all—typically because what it described was encompassed within the prior art. . . . Our prior cases have consistently applied prosecution history estoppel only where claims have been amended for a limited set of reasons, and we see no substantial cause for requiring a more rigid rule invoking an estoppel regardless of the reasons for a change.

Id. at 31-32. Thus, Amgen's evidence under the doctrine of equivalents is not defeated by the mere fact that Amgen's

amendment added the limitation that the claimed glycoprotein have the mature erythropoietin amino acid sequence of Figure 6.

The Court must instead endeavor to identify the reason such limitation was added. This search for purpose is made more difficult where, as here, there is nothing in the file wrapper as of the date of the amendment indicating that the claims were objectionable to the Patent Office. Such a notice followed by amendment would, of course, raise the inference that the subsequent amendment was intended to address the Patent Office's precise concern. Absent such clear history, however, the search for the purpose of the amendment becomes more thorny. Nonetheless, according to *Warner-Jenkinson*, Amgen bears the burden of showing that the amendment was not submitted "to avoid the prior art, or otherwise to address a specific concern—such as obviousness—that arguably would have rendered the claimed subject matter unpatentable." *Id.* at 30-31.

Reviewing the file wrapper, it appears that the amendment was submitted for the not uncommon purpose of distinguishing the language of the '080 claims from that of the glycoprotein claims of the '933 patent. By stating that the claims of the '080 patent "differ in scope from claim 1 of U.S. Patent 5,547,933 in specifying that the [claims of the '080 patent contain] the mature erythropoietin sequence of Figure 6," Trial Ex. 3 Tab 6 at 164, Amgen was simply directing the Patent Office to claim language that demonstrated that "same invention" type double patenting did not apply. By this amendment, Amgen was not attempting to distinguish the claims of the '080 patent from prior art because, due to the fact that both the '080 and the '933 patents arise from a common disclosure, the '933 patent is not prior to the '080 patent. Instead, Amgen was merely exercising its long-accepted right to press alternative claims covering different aspects of its invention.

Nor does Amgen's terminal disclaimer give rise to estoppel. Amgen filed a terminal disclaimer, causing the term of the '080 patent to end on the same day as the term of the '933 patent, for the purpose of mooting any possible non-statutory, obviousness-type double patenting rejection. *See id.* One might expect that such an attempt to avoid an objection relating to double patenting would be grounds for estoppel. Yet terminal disclaimers do not operate to effect estoppel: the filing of a terminal disclaimer simply serves the statutory function of removing the rejection of double patenting, and raises neither presumption nor estoppel on the merits of the rejection. *Quad Envtl. Techs. Corp.* v. *Union Sanitary Dist.*, 946 F.2d 870, 874 (Fed. Cir. 1991); *see also Wooster Brush Co.* v. *Newell Operating Co.*, No. 99-1393, 2000 WL 748074, at *5 (Fed. Cir. June 9, 2000) (unpublished opinion); *Sash Controls, Inc.* v. *Talon, L.L.C.*, Nos. 98-1152, 98-1182, 1999 WL 110546, at *3 (Fed. Cir. Jan. 27, 1999) (unpublished opinion).[40] There is no indication in the Federal Circuit's recent *Festo* decision that this limitation to estoppel is no longer good law. Without additional evidence, the Court will not infer from the terminal disclaimer that Amgen sought to overcome a meritorious prior art rejection.

At its core, what estoppel seeks to prevent is reliance upon the doctrine of equivalents when the prosecution history makes clear that the patentee abandoned the precise aspect of a competitor's product that infringes by equivalency. Only in this circumstance is it fair to limit the effective scope of the claimed invention. Simply put, the evidence does not show

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[40] For the propriety of citing an unpublished opinion, see *Anastasoff* v. *United States*, 223 F.3d 898, 899-905 (8th Cir.) (R. Arnold, J.) (holding that unpublished opinions have precedential effect), *vacated as moot*, No. 99-3917, 2000 WL 1863092 (8th Cir. Dec. 18, 2000), *Giese* v. *Pierce Chemical Co.*, 43 F. Supp. 2d 98, 103 (D. Mass. 1999) (relying on unpublished opinions' persuasive authority), and Richard S. Arnold, *Unpublished Opinions: A Comment*, 1 J. App. Prac. & Process 219 (1999).

that the patentee abandoned glycoproteins having a mature erythropoietin amino acid sequence of 165 residues for the purpose of avoiding prior art, obviousness, or any other patentability reasons. Thus, Amgen has met its burden under *Warner-Jenkinson.* As a result, the Court will not estop Amgen from contending that HMR4396 infringes the Figure 6 limitation by equivalency. Therefore, in light of its earlier findings that HMR4396 meets each limitation either literally or by an equivalent, the Court concludes that HMR4396 infringes the asserted claims of the '080 patent.

F. *The Remaining Defenses*[41]

It is appropriate again to pause for a moment to emphasize the importance of the particular procedural approach that this Court used in conducting the *Markman* hearing. Because this Court conducted its claim construction independent of rather than in the context of the infringement issues raised in the summary judgment hearing, it avoided any risk of conflating the legal issue of claim construction with the factual issue of infringement. This case provides an ideal example of the magnitude of the consequences of such conflation.

Had this Court constructed Amgen's claim language in the context of the issues of infringement, the risk of "neatly" disposing of the case by narrowly construing Amgen's claims would have loomed very large. Indeed, had the Court narrowly construed Amgen's claims, this already overlong opinion would have long been at an end because infringement would most likely have been decided on the summary judgment record, leaving TKT free and clear as a non-infringer and Amgen (though losing this case) would have retained its patent monopoly against all other comers.

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[41] It will be recalled that the Court rejected TK's anticipation and obviousness defenses at the close of its case pursuant to Federal Rule of Civil Procedure 52(c), setting out its findings and rulings in Section IV.D., at 75-110. TK's remaining defenses are addressed in this section.

However, by conducting its claim construction independent of the issues of infringement, this Court was not even tempted by such a narrow construction; rather, the Court properly performed its judicial function of legal construction by giving credence to the plain and ordinary meaning to one skilled in the art of Amgen's claims despite the breadth of such a construction.

It is only by walking the line strictly between legal construction and fact finding that this Court has stumbled upon the complex factual questions that are presented in this opinion. Now that the Court has found TKT to be an infringer under the Court's broad claim construction of Amgen's claims, that very construction provides TKT with a strong riposte—to destroy Amgen's patents entirely, even though this means opening the field to not only TKT, but also the world. The stakes in this phase of the battle are thus infinitely higher. Thus far, Amgen has largely secured the broad patent protection it has claimed.[42] A failure in this phase of the case could prove fatal, however, as it would extinguish Amgen's patent protection altogether.

As the contending parties sail into the culminating melee, however, Amgen is aided by two strong, though not impregnable, legal principles. First, as the owner of issued patents, Amgen is entitled to the "presumption of validity." The presumption of validity is, in patent law, not a true evidentiary presumption at all, i.e. an aid to proof that vanishes once the opponent produces evidence to rebut the presumed fact. Fed. R. Evid. 301; William G. Young et al., *Massachusetts Evidentiary Standards* 44 (2000); *see also*

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[42] Because it can be claimed that Amgen's broad patent monopoly serves as a "blocking" patent to prevent advances in research and development by others, some commentators claim that, in lieu of licensing, a doctrine of patent "fair use" ought be developed. *See, e.g.*, Maureen A. O'Rourke, *Toward a Doctrine of Fair Use in Patent Law*, 100 Colum. L. Rev. 1177, 1192-93 (2000).

Paul J. Liacos et al., *Handbook of Massachusetts Evidence* § 5.5.3, at 230 (7th ed. 1999). Rather, the presumption of validity shifts the burden of proof to TKT and places on it not only the burden of going forward but also the burden of persuasion itself. *See Canon Computer Sys., Inc.* v. *Nu-Kote Int'l, Inc.*, 134 F.3d 1085, 1088 (Fed. Cir. 1998). Moreover, in order to overcome the presumption of validity, TKT must convince the Court, not by a fair preponderance but by clear and convincing evidence, to adopt one or more of its defenses. *Sibia Neurosciences, Inc.* v. *Cadus Pharm. Corp.*, 225 F.3d 1349, 1355 (Fed. Cir. 2000). As will be seen in this most complex case, at least in part, it is this heightened standard of proof to which Amgen ultimately clings as a piece of flotsam among the wreckage of its evidentiary presentation.

1. Inequitable Conduct

TKT rigorously contends that Amgen's patents ought be declared unenforceable because they were obtained as a result of inequitable conduct. In order to obtain a patent, an applicant must first persuade the Patent Office, and more precisely its Examiner, that the applicant invented a patentable invention. During the course of this period of negotiation between the applicant and the Patent Office, the applicant provides significant information to the Patent Office in an attempt to prove that the patent should issue. As one might expect, for the Patent Office to determine intelligently whether a patent should issue, an applicant must disclose all information known to be material to patentability. Thus, when the applicant ultimately obtains the patent, but does so by either withholding material information from, or by misrepresenting material facts to, the Patent Office while possessing the intent to deceive the Patent Office, the patents are rendered unenforceable. *Baxter Int'l, Inc.* v. *McGaw, Inc.*, 149 F.3d 1321, 1327 (Fed. Cir. 1998).

To prove the defense of inequitable conduct, a defendant must show that the patentee withheld material information from the patent examiner or submitted false material information, with the intent to deceive or mislead the examiner into allowing the patent. *Upjohn Co.* v. *Moval Pharm. Corp.*, 225 F.3d 1306, 1312 (Fed. Cir. 2000) (citing *Kingsdown Med. Consultants, Ltd.* v. *Hollister Inc.*, 863 F.2d 867, 872 [Fed. Cir. 1988]). Both materiality and intent to deceive are independent elements, each of which must be proven by clear and convincing evidence. *See Kingsdown*, 863 F.2d at 872; *see also Manville Sales Corp.* v. *Paramount Sys., Inc.*, 917 F.2d 544, 552 (Fed. Cir. 1990). Information is material "'where there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent.'" *Upjohn*, 225 F.3d at 1312 (quoting 37 C.F.R. § 1.56 [1988] [amended 1992, 2000]); *see also Molins PLC* v. *Textron, Inc.*, 48 F.3d 1172, 1179 (Fed. Cir. 1995).[43] A reference, however, need not be disclosed to the examiner if it is merely cumulative of, or less material than, other references already before the examiner.

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[43] This formulation of the rule regarding materiality was in force from 1977 to 1992. In 1992 and again in 2000, the Patent and Trademark Office amended Rule 56. The rule, as amended in 1992, provided that:

> [I]nformation is material to patentability when it is not cumulative to information already of record or being made of record in the application, and (1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or (2) It refutes, or is inconsistent with, a position the applicant takes in: (i) Opposing an argument of unpatentability relied on by the Office, or (ii) Asserting an argument of patentability.

37 C.F.R. § 1.56(b) (1992) (amended 2000). The Federal Circuit, however, has made clear that this amendment is not retroactive. *See Molins*, 48 F.3d at 1179 n.8. As a result, because the prosecution of the patents-in-suit spanned the period from 1983 to 1999, and thereby straddled the amendment of Rule 56, the previous rule governs the conduct of Amgen's agents between 1983 and 1992 and the subsequent rule governs the conduct of Amgen's agents between 1992 and 1999.

Upjohn, 225 F.3d at 1312; *Baxter Int'l*, 149 F.3d at 1328. In assessing intent, the Court should consider any "evidence indicative of good faith." *Kingsdown*, 862 F.2d at 876. Finally, and importantly, the intent to deceive cannot be inferred "solely from the fact that information was not disclosed; there must be a factual basis for a finding of deceptive intent." *Hebert* v. *Lisle Corp.*, 99 F.3d 1109, 1116 (Fed. Cir. 1996). Each of TKT's various contentions will be addressed in turn.[44]

a. The Goldwasser Clinical Study

TKT contends that Amgen's representatives withheld from the Patent Office Dr. Goldwasser's urinary erythropoietin clinical study. TKT argues that the study was relevant to the patentability of Claim 1 of the '422 patent. In particular, TKT alleges that the study reveals that Dr. Goldwasser's urinary erythropoietin preparation contained a therapeutically effective amount of in vivo biologically active erythropoietin. As such, it constituted prior art that would have anticipated or rendered obvious Amgen's pharmaceutical composition claim had it been appropriately disclosed by Amgen's representatives. Consequently, contends TKT, Claim 1 of the '422 patent ought not be enforced.

The Court is not persuaded. Importantly, it appears to this Court that, although Amgen could have drawn more attention to the Goldwasser study, Amgen actually did disclose it. Specifically, during interference proceedings involving applications leading to the patents-in-suit, Amgen disclosed Dr. Goldwasser's sworn testimony before the United States

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[44] The Court recognizes that Amgen objects to TKT's pursuit of a number of separate allegations of inequitable conduct because, it argues, many of these allegations were not pled in the amended answer or otherwise timely disclosed to Amgen such that it could effectively prepare a defense. In light of the substantive outcome of these matters, however, resolution of this procedural dispute is unnecessary.

International Trade Commission ("ITC") to the Board of Patent Appeals and Interferences. In that testimony, Dr. Goldwasser described the unavailability of therapeutically effective amounts of EPO despite his abortive trial with human urinary erythropoietin. *See* Trial Ex. 209 at AM 17 027722-23. Furthermore, the ITC Administrative Law Judge, Sidney Harris, referred to this testimony in his Initial Determination Opinion. *See* Trial Ex. 101 at AM 17 027597. Amgen submitted Judge Harris' opinion to the Patent Office during prosecution and the Examiner, who was specifically provided with a copy, reviewed the opinion and cited its findings of fact as evidence demonstrating the non-obviousness of Dr. Lin's claimed compositions. *See* Trial Ex. 102 at AM 17 027580-81; Trial Ex. 109 at AM 27 015059; Trial Ex. 2198 at 214-15.

TKT replies, however, that Amgen may not rely upon its disclosure to the Interference Branch to satisfy its duty of disclosure during ex parte prosecution with an Examiner. *See Mech. Plastic Corp.* v. *Rawlplug Co.*, 14 U.S.P.Q.2d (BNA) 1058, 1061 (S.D.N.Y. 1989); *A.B. Dick Co.* v. *Burroughs Corp.*, 617 F. Supp. 1382, 1395 (N.D. Ill. 1985), *aff'd*, 798 F.2d 1392 (Fed. Cir. 1986); *Gen. Elec. Co.* v. *United States*, 206 U.S.P.Q. (BNA) 260, 280 (Ct. Cl. Trial Div. 1979). In *A.B. Dick*, for instance, an applicant failed to disclose material prior art during initial ex parte proceedings, cited the art during an interference, and then again failed to cite the art during post-interference ex parte prosecution. *A.B. Dick*, 617 F. Supp. at 1392-93. Interestingly, the examiner nonetheless learned of the art without the applicant's assistance. *Id.* at 1392. Notwithstanding the disclosure during the interference and that the examiner actually learned of the art on his own, the district court held that the subsequently issued

patent was unenforceable because of the applicant's failure to call the prior art to the examiner's attention:

> [I]nitial disclosure of prior art in the interference proceeding (as one of a large number of references in one of a large number of exhibits) does not satisfy the applicant's duty of candor—particularly where the prior art had been undisclosed for some years before that and later remained undisclosed by the applicant at the time he was urging issuance of the patent . . . .

Id. at 1397. The Federal Circuit affirmed, noting that "The PTO cannot realistically be thought of as the equivalent (say) of a small law firm office, in which notice to one person may fairly be deemed notice to all. It is not necessarily true that the PTO Examining Division will have access to proofs filed in the course of an interference." *A.B. Dick Co.* v. *Burroughs Corp.*, 798 F.2d 1392, 1399 n.7 (Fed. Cir. 1986) (quoting *A.B. Dick*, 617 F. Supp. at 1397).

This case is distinguishable, however, because here the prosecution history demonstrates that the Examiner reviewed and considered the Interference decision and record. After resolution of the Interference proceedings, Examiner David L. Fitzgerald recorded on the file wrapper of the application that led to both the '933 and '080 patents, that he had received and, for a two-month period, reviewed the Interference record and decision. The Examiner's notes state:

> Reviewed parent file 675,298
> Reviewed Interference file #102,334
> Reviewed published Intf. Decision (*Fritsch v. Lin*) & *Amgen v. Chugai* (18 U.S.P.Q.2d @1016)
> Oct-Nov 1993
> Fitzgerald DL

Trial Ex. 2 Tab 58 at 715. Subsequent notations indicate that the Examining Division understood the import of the Interference proceedings. *Id.* Tab 34 at 405; *see also id.* Tab 23 at 284-87. TKT responds by arguing that the Court should not

be persuaded that disclosure to Examiner Fitzgerald is sufficient since Examiner Martinell, rather than Examiner Fitzgerald, was the primary examiner involved in issuing the patents-in-suit. The *Manual of Patent Examining Procedure*, however, directs that a previous examiner's searches and actions must be given full faith and credit by all subsequent examiners. *Manual of Patent Examining Procedure* §§ 704, 706.04 (7th ed. 1998). Thus, unlike TKT's cited cases, the evidence here is clear that the Examining Division reviewed and considered the Interference record and the Board's decision. As a result, in this case as in others, disclosure to the Interference branch satisfied Amgen's duty of candor to the Patent Office. *See E.I. Du Pont de Nemours & Co.* v. *Phillips Petroleum Co.*, 656 F. Supp. 1343, 1376 (D. Del. 1987), *rev'd on other grounds*, 849 F.2d 1430, 1439 (Fed. Cir. 1988).[45]

Admittedly, Amgen neither submitted the actual scientific data relating to the study to the Patent Office nor extensively described the Goldwasser study in any of its submissions. Nonetheless, in this circumstance, its disclosures narrowly discharge its duty of candor. Beyond this, it is more than clear to this Court that Amgen's representatives, by their disclosures, were not deliberately hiding the study from the Examiner. Reference to the study was made, and if the Examiner believed that further inquiry was required, the Examiner could have pursued it—it was the Examiner's choice not to.

Moreover, the Goldwasser study is cumulative in the sense that Amgen had, in any case, clearly disclosed to the Patent Office that human urinary erythropoietin was biologically active in vivo. The patent itself discusses at length the

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[45] The Court also notes that the Board is the ultimate arbiter of matters of patentability within the Patent Office and the examiner is bound by the Board's decision. *In re Van Geuns*, 946 F.2d 845, 847-48 (Fed. Cir. 1991); *Dewez* v. *Schleimer*, 2 U.S.P.Q.2d (BNA) 1636, 1637 (Bd. Pat. App. & Interf. 1987); *see also* 37 C.F.R. § 1.198 (2000).

biological activity of natural human erythropoietin, including human urinary erythropoietin. *See* Trial Ex. 1 at 5:48-53, 5:67 to 6:5, 7:10-17, 33:19-31; 35; Trial Tr. at 2994:3-19, 2995:15 to 2996:10. The original filed Claim 41 also reveals that Amgen believed not only that urinary EPO was biologically active, but also that it had the same biological activity of Dr. Lin's invention. Trial Ex. 2 Tab 1 at 110. Furthermore, the prosecution history makes clear that the Patent Office understood that "naturally occurring EPO" included human urinary EPO. *See id.* Tab 4 at 163 ("The disclosure of Miyake et al., shows isolation and purification of naturally derived EPO."). The Patent Office initially rejected original Claim 41 on the basis that it was anticipated by Miyake, which concerns the purification of human urinary EPO. *Id.* at 156, 163; *see also* Trial Ex. 35 at 5558; Trial Tr. at 2998:21 to 3001:5, 3004:15 to 3005:2. Amgen agreed that its recombinant EPO and human urinary EPO had the same in vivo biological activity, but distinguished its EPO by differences in glycosylation as well as differences in therapeutic effectiveness in treating patients with anemia. *See* Trial Ex. 2 Tab 6 at 175, 181-82; *id.* Tab 11 at 224, 227. Amgen also amended Claim 41 to highlight the specific in vivo biological activity characteristics shared by human urinary EPO and the recombinant EPO. *See id.* Tab 6 at 172. In light of this evidence, it seems clear that the Patent Office understood that recombinant and urinary EPO shared common in vivo biological effects. As a result, even if the Court agreed that Dr. Goldwasser's study showed a meaningful increase in reticulocyte and red blood cell production (a point which has not sufficiently been proven), it would have merely been cumulative.

Moreover, the Goldwasser study is not particularly material. At least two specific limitations of Claim 1 of the '422 patent essentially exclude Dr. Goldwasser's work. As the Court has previously explained, there is no evidence that Dr. Goldwasser's urinary EPO went beyond biological activity and accomplished therapeutic effectiveness, which is required

by Claim 1 of the '422 patent.[46] *See supra* Section IV.D.1.c, at 94-98. Likewise, Dr. Goldwasser's study did not involve an EPO purified from mammalian cells grown in culture, which is also required by Claim 1 of the '422 patent. Thus, in at least these two respects, Dr. Goldwasser's study was immaterial to the claim TKT seeks to defeat.

Most importantly, TKT has failed to produce any persuasive evidence that causes the Court to doubt the integrity of the individuals who bore the duty of shepherding the Amgen patent applications through the Patent and Trademark Office. Consequently, its charge of inequitable conduct utterly fails. Dr. Lin testified that he knew that Dr. Goldwasser had administered urinary EPO to two patients, but based upon the information that Dr. Goldwasser provided him, Dr. Lin concluded that urinary EPO was not therapeutically effective. *See* Trial Tr. at 947:21 to 948:12, 1097:1-14, 1098:8 to 1099:15, 1102:5 to 1103:2. In addition, those responsible for prosecuting the patents learned about the Goldwasser study from Dr. Goldwasser's testimony before the ITC, which highly criticized the value of the study. *See* Trial Ex. 209 at 22-24; Trial Tr. at 2925:9-21, 2961:19 to 2963:11. That the prosecuting attorneys understood that the Goldwasser study was a therapeutic failure negates an alleged intent to deceive. In fact, these attorneys actually disclosed the results of the study precisely because, in their minds, the failed test revealed a long felt need for therapeutically effective erythropoietin therapy. Thus, the Court finds that

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[46] In an attempt to escalate the materiality of the Goldwasser study vis-a-vis Claim 1 of the '422 patent, TKT conflates biological activity with therapeutic effect. In short, TKT contends that because the Goldwasser study presents data regarding the biological activity of human urinary EPO and since biological activity is equivalent to therapeutic effects, the Goldwasser study was highly relevant to the patentability of the claimed pharmaceutical composition. This conflation, however, is inappropriate, for these two phrases, though related, have entirely independent meanings. *See supra* Section IV.D.1.c, at 94-98.

Amgen provided the Goldwasser testimony and the ITC decision to the Patent Office because it believed that these sources revealed that a therapeutically effective erythropoietin product had not yet been obtained. Trial Tr. at 2963:1-11, 2969:16 to 2970:2. There was no intent to deceive. As a result, the Court concludes that TKT has failed to prove by clear and convincing evidence that Claim 1 of the '422 patent ought not be enforced because it was issued due to inequitable conduct on the part of Amgen's agents.

b. *Data Concerning Glycosylation Differences*

TKT also argues that the '933 patent should be rendered unenforceable because Amgen misrepresented some material data and withheld other experimental data relating to glycosylation differences between recombinant and human urinary erythropoietin. Claim 1 of the '933 patent covers erythropoietin glycoprotein products having glycosylation which differs from that of human urinary erythropoietin. TKT contends that Amgen's counsel knew that certain tests revealed that recombinant and human urinary EPOs were glycosylated to the same extent, but nonetheless failed to disclose these tests to the Patent Office. Instead, Amgen continued to stand by its representations in the patent and press claims asserting glycosylation differences. *See* Trial Ex. 1 at 28:33-50; Trial Ex. 2161 at 8-9; Trial Ex. 2164 at 4; Trial Tr. at 2862:5-18, 2879:12-25. If, indeed, these tests truly revealed that there were no detectable glycosylation differences between the two types of EPOs, then TKT will have satisfied its burden of proving materiality by clear and convincing evidence.

In November of 1984, Mr. Michael F. Borun, Amgen's patent counsel, received a package of information from Dr. Joan Egrie that was later placed in a folder labeled "Egrie Input." Trial Ex. 2400; Trial Tr. at 2836:9 to 2838:4, 2848:7-22. The Egrie Input included an SDS-PAGE gel that compared COS-1 produced recombinant EPO and Goldwasser's human urinary EPO standard. Trial Ex. 2400 at 20; Trial Tr.

at 2840:2 to 2841:10, 2842:9-16. Dr. Egrie reported that these EPOS "have the same molecular weight" and "that the recombinant EPO is glycosylated to the same extent as the native protein." Trial Ex. 2400 at 17, 22 ("Size of Gene's std. ~= size of COS cell-produced EPO as was seen in the prior sections . . . ."). The Egrie Input also included SDS-PAGE gels comparing CHO cell produced recombinant FPO and Lot 82 human urinary EPO; she explained that these gels indicated that the differing EPOs had the same molecular weight. *Id.* at 5a, 9, 22 ("CHO cell material . . . is ~ to Lot 82 EPO."). TKT contends that both of these tests were material to patentability and were intentionally shielded from the eyes of the Examiner even as Amgen's representatives were arguing to the Patent Office that glycosylation differences were apparent. TKT contends that this misrepresentation was compounded by Amgen's failure to correct the erroneous carbohydrate constitution values disclosed in the patent. Trial Ex. 1 at 28:51-57.

TKT also points to a number of Amgen publications that likewise reported that recombinant EPOs and human urinary EPOs migrated identically on SDS-PAGE gels and had the same molecular weight, suggesting that they were glycosylated the same. Trial Ex. 2406 at 243, 248-49 (Vapnek study); Trial Ex. 2398 at 218 (Egrie study); Trial Ex. 137 at 696-98 (Browne study). TKT also argues that some of Amgen's FDA submissions contradicted its arguments to the Patent Office. Trial Ex. 2023(b) at A 45481, A 45545 Fig. 50-20, A 45557 Fig. 50-26. The inference pressed by TKT is that Amgen, on the one hand, sought to put the FDA at ease by claiming that the glycosylation of CHO-produced recombinant EPO was just like that of naturally-occurring human urinary EPO, but on the other hand, attempted to persuade the Patent Office that recombinant EPO was truly novel over human urinary EPO by pointing to glycosylation differences.

Amgen responds to these charges. First, the Egrie Input was disclosed and considered by the Patent Office. In particular, Mr. Borun testified that it had been disclosed during the *Fritsch* v. *Lin* Interferences and used as an exhibit in the *Amgen* v. *Chugai* litigation. Trial Tr. at 2863:9 to 2864:4; *see also* Trial Ex. 105 (Egrie Input File, DX 316 in Civ. Action No. 87-2617-Y); Trial Ex. 206 at AM 17 057546-54, AM 17 05635-59 (Notice pursuant to 37 C.F.R. § 1.682[a] and Offer of Official Record Regarding Testimony of Egrie and Attachments submitted to the Patent Office in the Interferences). For example, Amgen submitted to the Board of Patent Appeals and Interferences a declaration of Dr. Egrie describing her various experiments, including the disputed SDS-PAGE experiments and the relevant laboratory notebook excerpts. Trial Ex. 2309 at AM 17 034807-09; *see also* Trial Exs. 104, 216, 217, 2118 (Lin Exs. 114-17 from *Fritsch* v. *Lin*, Interference Nos. 102,096, 102,097, and 102,334). Lin's Exhibit 115, for example, included pages sixty-five to seventy of Egrie Laboratory Notebook No. 633, Trial Ex. 104, and page sixty-nine of this notebook showed results from comparisons between CHO-produced EPO and various uEPO products. *Id.* at AM 17 079278. As already determined, Amgen's disclosure during the Interference proceedings discharges its duty of disclosure to the Examining Division as well.

Amgen also denies TKT's claim that it failed to disclose publications concluding that rEPO and uEPO glycosylation are the same. In an amendment filed on February 16, 1995, Amgen included a declaration by Dr. Cummings and attached a copy of the Browne publication, which TKT alleges was withheld from the Patent Office. Trial Ex. 210 at AM 27 020914, AM 27 020922, AM 27 021116. The Browne publication in turn cites an Egrie publication. *Id.* at AM 27 021119. The Browne publication explains that rEPO produced from both COS-1 and CHO cells "migrate identically" or are "indistinguishable." *Id.* at AM 27 021119, AM 27 021121. Amgen repeatedly cited this publication throughout

the prosecution of the patents-in-suit. Trial Ex. 3 Tab 7 at 182; Trial Ex. 4 Tab 10 at 181; Trial Ex. 5 Tab 10 at 209; Trial Ex. 6 Tab 27 at 266-501; Trial Ex. 6 Tab 36 at 559; Trial Ex. 137 Fig.4. Furthermore, in his declaration, Dr. Cummings discussed the Egrie publications and stated that the gels therein showed only that rEPO and uEPO were "similar but not identical" in their migration on SDS-PAGE. Trial Ex. 210 at AM 27 020644. The Court finds that in specifically identifying the Browne publication and discussing the Egrie publications, Amgen informed the Patent Office that these tests (and the conclusions derived therefrom) were circulating within the field.[47]

Additionally, Amgen made disclosures regarding rEPO and uEPO migrating identically during the Interference proceedings. Trial Ex. 97 (Interference Lin Ex. 218); Trial Ex. 111 (Interference Lin Ex. 396); Trial Ex. 112 at AM 17 028197-208 (Lin's Notice IV submitted in Interferences); Trial Ex. 113 at AM 17 024642-57 ("Publication 16," attached to Lin's Notice IV); Trial Ex. 218 (Notice IV by Lin submitted in Interferences). Moreover, although the ultimate issue for determination differed, the same allegations made here by TKT with respect to Dr. Egrie's work were resolved in favor of Amgen by the Patent Office during the Interference proceedings. *Fritsch* v. *Lin*, 21 U.S.P.Q.2d (BNA) 1739, 1741-42 (Bd. Pat. App. & Interf. 1991); Trial Ex. 110 at 36 (8/12/91 Fritsch Reply Brief, Paper No. 169 in Interference No. 102,334); Trial Ex. 214 at AM 17 003716 (Fritsch Proposed Findings of Fact VI-17 at 227). Importantly, as explained above, the prosecution history reveals that the Examining Division of the Patent Office reviewed the

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[47] In any event, there is considerable doubt that the authors' conclusions were justified in light of the gels. *See, e.g.*, Trial Ex. 137 at 698; Trial Ex. 2399 at AM 49 028390; Trial Ex. 2398 at AM 47 012012-13; Trial Tr. at 684:4 to 686:15, 746:12 to 757:20, 1048:25 to 1057:24, 2379:10 to 2384:8.

Interference record and the Board's decision, as it is required to do.

As for the allegations regarding disclosures to the FDA, Amgen points out that the same gel that had earlier been submitted to the FDA (as well as the related conclusion that rEPO and uEPO migrate identically) was disclosed in the 1986 Egrie publication during the Interference. Trial Ex. 218 at AM 17 028197-208 (Lin Notice IV attaching Egrie et al., 172 *Immunobiology* 213-24 [1986]); *see also* Trial Ex. 207 at AM 17 049294-314 (Fritsch Ex. 399 from *Fritsch* v. *Lin*, Interference Nos. 102,096, 102,097, and 102,334). TKT's expert witness, Dr. Phillips W. Robbins also admitted that Amgen later told the FDA that there were differences in glycosylation between its rEPO and uEPO. Trial Tr. at 1999:10 to 2001:5. Thus, TKT's representation that Amgen was maintaining self-serving and conflicting messages to the FDA and the Patent Office is itself somewhat misleading.

At the same time, TKT has provided no evidence tending to show that the SDS-PAGE data set out in the patent was false or misleading. Mr. Borun received the data from Dr. Lin or members of Dr. Lin's staff and after Mr. Borun drafted the patent application, Dr. Lin reviewed and approved it. Trial Tr. at 1060:5-13, 2831:8-17, 2846:1-10, 2850:2-7; Borun Dep. at 26-27, 69-71. Mr. Borun, meanwhile, has no recollection of the Egrie Input document, which was produced from the files of his firm. Trial Tr. at 2836:37, 2848:7-22. In asserting the charge of inequitable conduct against Amgen, TKT is contending that Mr. Borun's lack of memory is deviously convenient. The Court is not persuaded that Mr. Borun has or had any such devious designs.

In any event, all of TKT's arguments surrounding the SDS-PAGE data are premised on one erroneous notion: that two EPOs that migrate identically on SDS-PAGE necessarily have the same glycosylation. Not so. As explained in the '933 infringement section of this decision, *supra* Section IV.E.2,

at 128-39, without additional SDS-PAGE tests comparing deglycosylated EPOS, one cannot make the more relevant determination as to glycosylation differences. Indeed, TKT's witness, Dr. Matsudaira, agreed that two EPO samples that migrate identically on SDS-PAGE do not necessarily have identical glycosylation. Trial Tr. 2372:22 to 2373:4. Moreover, the patent itself teaches that these subsequent tests should be performed. Trial Ex. 1 at 28:42-50. Importantly, portions of the Egrie Input ignored by TKT actually show an SDS-PAGE gel that compares CHO and COS-1 rEPOs with Goldwasser's uEPO both before and after at least partial deglycosylation. Trial Ex. 2093 at AM 87 015712; Trial Ex. 2400 at A95580; Trial Tr. at 2384-86. In reviewing this gel before partial deglycosylation, Dr. Egrie concluded that the "size of the CHO cell material is larger than COS or Gene's std." Trial Ex. 2400 at A95579 (22); Trial Tr. at 2384:2 to 2388:12; 2841:2-10. Then, after partial deglycosylation using neuraminidase treatment to remove the sialic acids, Dr. Egrie determined that "COS & CHO neuraminidase digestion products are both larger in size than digestion product obtained for Gene's crude EPO. This may suggest that there are differences in the remainder of the carbohydrate backbone of the recombinant material vs. Gene's std." Trial Ex. 2400 at A95579 (22); Trial Tr. at 2851:2-20. Thus, as both the patent and even the Egrie Input teach, one must perform SDS-PAGE tests not only before, but also after deglycosylation treatment to obtain information about the glycosylation of glycoproteins. Contrary to TKT's contentions, then, data in the Egrie Input is actually consistent (or at least not inconsistent) with Amgen's representations in the patent specification. Trial Ex. 126 at 69; Trial Ex. 2400 at A95591 (9), A95579 (22); Trial Tr. at 675:3 to 677:24, 2389:19 to 2390:1; *see also* Trial Ex. 2083 at 5005649-56 (69-72); Trial Tr. at 2385:3 to 2387:4, 2388:3 to 2390:1. Moreover, of particular significance here because the tests relied upon by TKT compare

only glycosylated EPOs, they are inconclusive and hence immaterial to the question of glycosylation differences.[48]

In addition, the erroneous nature of certain carbohydrate constitution values was disclosed through the Interference record to, and presumably considered by, the Patent Office. At the time the application was submitted, Dr. Lin and Mr. Borun believed the data to be accurate. Trial Tr. at 979:14 to 981:2, 2854:9-20, 2856:13 to 2857:2, 2859:10-17. During the Interference, the Board was informed that this carbohydrate data was incorrect. Trial Ex. 107 at AM 17 016877 (Brief for Senior Party Lin, Interference No. 102,334); Trial Ex. 110 at 42-43 (July 8, 1991 Brief for the Party Fritsch, Interference No. 102,334); Trial Tr. 1094:4-8; Borun Dep. (Nov. 23, 1999) at 146:17 to 147:8; *see also* Trial Ex. 214 at 223-25 (Fritsch Proposed Findings of Fact VI-6 to VI-12). Having the issue directly presented to it, the Board of Patent Appeals and Interferences determined that, despite the apparent error, "Lin's involved application, in addition to including the disputed hexose molar ratio data, also reports results of Western blot and SDS-PAGE analyses . . . coupled with results of endoglycosidase F enzyme treatment which . . . support the conclusion that there is indeed a difference in carbohydrate composition . . . ." *Lin*, 21 U.S.P.Q.2d (BNA) at 1741-42. The '933 prosecution history reveals that the Examining Division reviewed the Interference record and the Board's decision. Trial Ex. 2 at 284-87, 715. Amgen also informed the Patent Office that Genetics Institute, on appeal, had accused Amgen of inequitable conduct for failing to disclose the

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[48] Another test relied upon by TKT compares CHO material with Goldwasser and Lot 82 uEPO preparations. Trial Ex. 1 at A95578 (5a). Yet aided by the testimony of Drs. Cummings and Matsudaira, the Court finds that the CHO-expressed EPO did not migrate the same as the urinary EPOs. Trial Tr. at 676:2 to 677:24, 2388:3 to 2390:1; *see also* Trial Ex. 2 Tab 7, at 191 (Strickland Decl. [Nov. 30, 1988]); Strickland Dep. at 412-15.

erroneous nature of the carbohydrate data. Trial Ex. 205 at AM 17 011480-82 (Mar. 6, 1992 Petition under 37 C.F.R. § 1.182 at 10-12); Trial Tr. at 2986:24 to 2989:2. In addition, the Examiner also had before him the correct carbohydrate data for CHO-cell produced human EPO and uEPO provided in the Takeuchi and Sasaki references. Trial Ex. 2 at 448 (Aug. 16, 1994 Examiner's Action); Trial Ex. 210 at AM 27 020935-37, AM 27 021007-13, AM 27 021037-54 (Feb. 16, 1995 Amendment). Drs. Cummings and Robbins also agreed that the data was "grossly inaccurate" and that the error would have been readily identified by one of skill in the art in 1984. Trial Tr. at 622:19 to 624:6, 2130:20 to 2131:3. Furthermore, because the Patent Office had the correct carbohydrate constitution data as well as additional data confirming glycosylation differences, the incorrect data was immaterial to the patentability of the '933 claims. *Fritsch*, 21 U.S.P.Q.2d (BNA) at 1741-42; Trial Ex. 2 Tab 38 at 448; Trial Ex. 210 at AM 27 020935-37, AM 27 021007-13, AM 27 021037-54.

In light of the disclosures made directly to the Patent Office as well as those made indirectly through the Interference record, it is hard to believe that the Examiner was somehow left in the dark about the glycosylation differences dispute. Amgen presented significant data to the Examiner suggesting glycosylation differences and also disclosed apparently conflicting data. What more can Amgen fairly be expected to do? At some point, the applicant must be permitted the opportunity to argue that some data is more worthy of reliance than other data. Instead, TKT implies that Amgen should have stood by less reliable and incomplete data rather than data obtained from both glycosylated and deglycosylated EPOs. This expectation is unreasonable.

Thus, the Court finds that Amgen complied with its duty of candor with respect to data regarding glycosylation differences. Nonetheless, even if Amgen had withheld this data from the Patent Office, such withholding would not give rise

to a charge of inequitable conduct because TKT has failed to prove by clear and convincing evidence that this data was material or that it was withheld with the intent to deceive.

c. *The Human '293 Cell Experiments*

TKT also contends that the '422 and '349 patents should be rendered unenforceable because Amgen failed to disclose that its human host cell experiments performed with '293 cells were unsuccessful in producing high levels of EPO. Trial Tr. at 2974:12-17. In January of 1984, Amgen scientists measured EPO produced in both COS-1 and human cells referred to as '293 cells. The '293 cells produced about one hundred times less EPO than the COS-1 cells. Trial Ex. 2410 at AM 47 037787-88. While the COS cell data was added to the patent specification, the '293 cell data was not. Trial Tr. at 965:8 to 967:19. Amgen, however, continued to pursue claims like Claim 1 of the '422 patent which, Amgen argued, covered "any polypeptide having the amino acid sequence of EPO isolated from human urine and may be produced in human cells or in any other mammalian cells." Trial Ex. 2215 at AM 27 068753. TKT argues that Amgen withheld these '293 experiments because they would have cast significant doubt upon its assertion that its invention extended not only to CHO and COS cells but also to all mammalian cells including human cells.

As the Court will explain, contrary to TKT, the purpose of the '293 cell experiments was not to produce EPO in abundance, as TKT's argument implies. *See infra* Section IV.F.4.c, at 239-41. Instead, the purpose of the transient transfection experiments was to obtain a quick determination that Dr. Lin had, indeed, cloned the DNA sequence encoding human EPO. Trial Tr. at 428:10 to 429:12, 967:3-18, 1112:16 to 1113:11, 2111:19 to 2112:4, 2556:11 to 2556:3-8, 2559:1-6, 2568:8 to 2569:8, 2572:25 to 2573:4. Based upon Dr. Jeffrey Browne's contemporaneous notation of "Eureka," which he wrote in his laboratory notebook as he recorded the

results of the human cell experiments, it is clear to this Court that the experiments achieved their intended purpose. Trial Ex. 2350 at A 13932; *see also* Trial Tr. at 2111:19 to 2112:4, 2559:2-6, 2565:1 to 2567:25. If the goal of the experiments were high level expression, one of skill in the art would have known to employ the other techniques taught in the Amgen patent, such as the use of selectable markers, amplification, and sub-cloning. *See Johns Hopkins Univ.* v. *CellPro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998); *Atlas Powder Co.* v. *E.I. Du Pont de Nemours & Co.*, 750 F.2d 1569, 1577 (Fed. Cir. 1984). Thus, these tests were not material to whether Amgen ought—as a matter of equitable conduct—be permitted to pursue cell and pharmaceutical claims that reach human cells. As will be seen, however, the question of enablement is a much closer one.

Moreover, Amgen disclosed the '293 experiments. Amgen repeatedly disclosed the decision in *Amgen, Inc.* v. *Chugai Pharm. Co.*, 13 U.S.P.Q.2d (BNA) 1737 (D. Mass. 1989) (Saris, M.J.), *aff'd in part, vacated in part*, 927 F.2d 1200 (Fed. Cir. 1991). Trial Ex. 2 Tab 19 at 267; Trial Ex. 215 at AM 17 007065, AM 17 007068; Trial Tr. at 2925:22 to 2926:6. In her decision, Judge Saris explicitly refers to the '293 experiments and the fact that they successfully produced human EPO. She wrote, "By January 10, 1984, Amgen had expressed human EPO in human embryonic kidney cells called '293' cells . . . ." *Amgen*, 13 U.S.P.Q.2d (BNA) at 1748. Furthermore, during the Interference proceedings, Drs. Egrie and Browne submitted declarations to the Board in which they described these experiments and pointed the Board to the relevant laboratory notebooks. Trial Ex. 213 at AM 17 079613 (79) (Lin Ex. 112, Doc. Nos. L00982-85, L01001-05 [J. Egrie Laboratory Notebook No. 540 ("Transient Transfection in 293 hEPO—Are seeing expression!")]); Trial Ex. 217 at AM 17 009866 (Lin Ex. 116, Doc. Nos. L01101-04 [J. Lane Laboratory Notebook]); Trial Ex. 2116 (Lin Ex. 113, Doc. Nos. L01080-86 [J. Egrie's Laboratory

Notebook No. 569]); Trial Ex. 2032 (Mar. 18, 1991 Browne Decl. ¶¶ 7-15); Trial Ex. 2309 at AM 17 0034781-82, AM 17 034784-86 (Mar. 18, 1991 Egrie Decl. ¶¶ 5, 8-10). Recall that the Examiner reviewed the Interference record. Thus, the '293 experiments were actually disclosed to the Patent Office.

Even had Amgen withheld the '293 experiments from the Examiner and these allegedly unsuccessful experiments had been—as appears to be the case—material to patentability, the Court finds no evidence of an intent to deceive on the part of Amgen's representatives. Because these experiments achieved their purpose, Amgen's patent counsel, Mr. Stuart Watt, never believed that there was any reason to discuss these experiments with the examiner. Trial Tr. at 2974:12-17. The Court, therefore, concludes that if any material non-disclosure occurred, it did not occur for the intended purpose of deceiving the Patent Office into issuing patents covering human cells. Consequently, TKT's inequitable conduct defense fails with respect to the '293 cell experiments.

d. *The Present Litigation*

TKT also asserts that the '349 and '422 patents should not be enforced against it because Amgen withheld from the Patent Office not only that the patents-in-suit were the subject of litigation, but also that TKT's allegations in the lawsuit went right to the issue of patentability. The *Manual of Patent Examining Procedure* recommends disclosure of the existence of any lawsuit and any information from the lawsuit that is material to a patent application. *Manual of Patent Examining Procedure* § 2001.06 (7th ed. 1998). At the time the lawsuit was filed on April 15, 1997, only the '698, '080, and '933 patents had been issued. Trial Exs. 2-6. Amgen directly informed the Patent and Trademark Office of this lawsuit by letter the day after the complaint was filed. Trial Ex. 204 (Apr. 16, 1997 Peterson letter). In addition, Amgen filed a notice pursuant to 35 U.S.C. § 290 with the Clerk of the District Court of Massachusetts. Docket No. 6; *see also*

Haney v. *Timesavers,* 900 F. Supp. 1378 (D. Or. 1995). According to the statute, the Clerk is then required to give written notice to the Commissioner, "setting forth so far as known the names and addresses of the parties, name of the inventor, and the designating number of the patent upon which the action has been brought." 35 U.S.C. § 290. The Commissioner then is required to enter the receipt of such notices in the file of the relevant patent or patents. *Id.* What galls TKT here is that this notice only made reference to the '698, '080, and '933 patents, since they were the only patents-in-suit at the time. TKT argues that, because Amgen never told the Patent Office that the complaint was later amended to add charges of infringement of the '349 and '422 patents, Amgen acted unfairly. The Court is not convinced.

Initially, the Court notes that the Clerk actually bears some responsibility for disclosing additional patents-in-suit. The statute specifically states that "[i]f any other patent is subsequently included in the action [the Clerk] shall give like notice thereof." 35 U.S.C. § 290. Thus, although the duty of candor ultimately falls on the shoulders of the patent applicant, it seems reasonable for an applicant to expect that a court officer will perform statutory requirements.

Most importantly, TKT has not even begun to demonstrate that Amgen representatives possessed an intent to deceive the Patent Office in failing to provide specific notification regarding this litigation. With respect to its duty to disclose this litigation, Amgen's in-house counsel, Mr. Watt explained that he believed that Amgen satisfied its duty of disclosure by submitting the earlier notice. Trial Tr. at 2980:16, to 2983:22, 2985:24 to 2986:20, 3026:18 to 3027:10. Mr. Borun similarly testified. *Id.* at 2909:25 to 2910:14; 2913:8-25, 2915:7-21, 2921:5-16. The Court believes their testimony. Thus, even if the Court were to conclude that Amgen neglected its duty of candor in failing to update the Patent Office regarding this

litigation, TKT has failed to prove by clear and convincing evidence that Amgen did so with the intent to deceive.

In summary, TKT's proof of inequitable conduct with respect to each of these charges falls short of the mark. Although the directness of Amgen's disclosures varies depending on the particular piece of disputed information, one truth remains the same throughout: Amgen's representatives never intended to deceive the Patent Office. Consequently, a finding of inequitable conduct would be error and the Court does not so find on the complete trial record here.

2. *Written Description*

The first paragraph of 35 U.S.C. § 112 provides the basic requirements for the content of a patent specification:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains . . . to make and use the same . . . .

35 U.S.C. § 112 (1998). The sufficiency of the disclosure is measured as of the time of its filing. *Reiffin* v. *Microsoft Corp.*, 214 F.3d 1342, 1346 (Fed. Cir. 2000) (quoting *Application of Glass*, 492 F.2d 1228, 1232 [Ct. Cust. Pat. App. 1974])." The purpose of this provision is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification." *Id.* at 1345. In order to serve this policy purpose, "the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989). Thus, section 112 requires this Court to determine whether Amgen's specification, considered as a whole, conveys to one of ordinary skill in the art either explicitly or inherently, that Dr. Lin invented the subject matter claimed in the patents-in-

suit. *Reiffin*, 214 F.3d at 1346; *see also Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991).

Of great significance here, however, once the Patent and Trademark Office issues the patent, the presumption of validity takes hold, *see* 35 U.S.C. § 282, requiring the Court to presume that the specification adequately describes the claimed subject matter. As a result, the burden falls upon TKT to prove by clear and convincing evidence that the specification fails to describe Amgen's claimed inventions. Although TKT persuades the Court by a preponderance of the evidence that the specification is deficient in some regards, it fails to make its case by clear and convincing evidence. Consequently, Amgen's patents narrowly survive TKT's written description challenge.

a. *'422 Patent*

As to the '422 patent, the Court initially disposes of those limitations that are clearly adequately described in the '422 patent. First, various passages of the specification explicitly address the characteristics of the claimed pharmaceutical composition. In the "Brief Summary" portion, the specification provides:

> Also comprehended by the invention are pharmaceutical compositions comprising effective amounts of polypeptide products of the invention together with suitable diluents, adjuvants and/or carriers which allow for provision of erythropoietin therapy, especially in the treatment of anemic disease states and most especially such anemic states as attend chronic renal failure.

Trial Ex. 1 at 12:1-7. Thus, one of ordinary skill in the art in 1984 would understand this paragraph to describe generally the pharmaceutical composition claimed in the '422 patent. *See* Trial Tr. at 1915:21 to 1916:23. In addition, other portions of the specification provide specific information regarding effective dosages and therapeutic effect in mice.

Trial Ex. 1 at 28:16-27, 33:50-61. Second, additional passages describe the purification of erythropoietin products from the host cell cytoplasm, membranes, or cell culture media. *See id.* at 11:8-14, 27:15-50, 28:29-32, 37:43-49. One of skill in the art in 1984 would have understood the Lin patent to describe techniques to obtain purified erythropoietin. Trial Tr. at 193:4 to 194:3. Third, the specification makes reference to various possible diluents, adjuvants, and carriers that could be used for delivery of erythropoietin therapy. Trial Ex. 1 at 33:61 to 34:27. One of ordinary skill in the art would have understood from these passages that Dr. Lin possessed the invention claimed in the '422 patent. The specification's detailed description of these elements quickly defeats TKT's contention that the written description is inadequate, save for one critical element that demands further analysis: mammalian cells.

Claim 1 of the '422 patent claims a pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin which has been purified from *mammalian cells* grown in culture. Trial Ex. 6 at 38:39. TKT argues that the specification fails to describe EPO production from all mammalian cells.

The Court recognizes that Claim 1 of the '422 patent does not claim pharmaceutical compositions containing erythropoietin expressed from *all* mammalian cells, but only mammalian cells *grown in culture. Id.* at 38:39-40. Moreover, the Court finds that, based upon the knowledge possessed by one skilled in the art as well as the teachings in the specification, one of skill in the art in 1984 would have known to select one of the many mammalian cells that were available and suitable for continuous growth in culture in order to produce high levels of a desired protein. *See* Trial Tr. at 2671:21 to 2672:6; *see also id.* at 514:22-25.

Nonetheless, the Court agrees with TKT's central contention that the specification—at least explicitly—reports

production of EPO in host cells of only two mammalian species. Trial Ex. 1 at 23:4-15, 25:35-36, 25:39-42, 26:11-15. Examples 7 and 10 describe human erythropoietin production in monkey (COS-1) and hamster (CHO) cells, respectively. Trial Ex. 1 at 23:1 to 24:38, 25:29 to 29:7. Thus, the key question is squarely posed: do detailed descriptions of EPO production in these two mammalian species cell lines inform those skilled in the art that Dr. Lin possessed an invention encompassing EPO production in all mammalian cells grown in culture? After much reflection and despite some hesitancy, the Court concludes that they do.

The Court finds that the specification places all competitors on notice that its invention was not limited to erythropoietin products obtained only from COS-1 and CHO cells. For example, the specification announces that the invention contemplates the expression of polypeptides in eucaryotic hosts including "mammalian cells in culture" and refers to products of expression in "vertebrate (e.g., mammalian and a[v]ian) cells . . . ." *Id.* at 10:15-27. Furthermore, there is a genuine dispute between the expert witnesses who testified in this case regarding whether one skilled in the art in 1984 would understand that Dr. Lin's invention reached EPO produced in all mammalian hosts grown in culture. With respect to this dispute, the Court credits the testimony of Amgen's witnesses. On the first day of trial, Dr. Harvey Lodish explained that Example 10 "teaches that one can use vertebrate cells, mammalian cells in this process." Trial Tr. at 140:6-7. He continued, "[o]ne of ordinary skill in the art, me, my students, would have understood this not to be limited to the specific types of cells that we[re] used in this example, that other vertebrate cells, mammalian cells, could have been used." *Id.* at 140:7-11. After being asked to review other sections of the specification, Dr. Lodish explained that the Lin patent disclosed to those of ordinary skill in the art as of 1984 "that many types of vertebrate mammalian cells could be used" to produce EPO. *Id.* 251:3-12. He added definitively

that the "techniques described in the Lin patent are equally applicable to [mammalian] cells, other than COS or CHO cells, without question." *Id.* at 251:18-20. During an exchange with the Court, Dr. Lodish elaborated, explaining that one skilled in the art would infer from the examples using COS-1 and CHO cells that similar outcomes could be expected from other mammalian cells "[b]ecause these cells, vertebrate cells, mammalian cells specifically, make proteins and process them in substantially the same way." *Id.* at 141:16-18. Dr. Lodish did admit that "there may be minor differences, but those would be easy to figure out experimentally." *Id.* at 141:19-20. Thus, "with a strong likelihood of success, one could have used cells other than the CHO cells or the COS cells that he used in this patent." *Id.* at 141:20-23. Consistent with Dr. Lodish's testimony, Dr. Thomas Randolph Wall testified that the "teachings of the Lin patent describe vertebrate mammalian cells, and the techniques are all applicable to human cells which can be grown in culture." *Id.* at 2623:22-25. Consequently, the Court concludes that one of ordinary skill in the art in 1984 would have understood the teachings of the patent specification to encompass pharmaceutical compositions containing human erythropoietin purified from all mammalian cells grown in culture.

TKT's arguments that the Lin specification only teaches exogenous[49] EPO DNA expression systems and not endogenous EPO DNA expression systems does not alter this conclusion. While it is true that TKT put forth concrete documentary and testimonial evidence tending to show that Amgen's invention was limited to the expression of exo-

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[49] As previously explained, exogenous DNA is DNA that does not originate in the host cell into which it is inserted or transfected. Trial Tr. at 2619:18-19. It is DNA that has been removed from the cell in which it originated, placed in a vector, and reintroduced into a host cell. *Id.* at 1330:2-5.

genous DNA,[50] even if the Court were to assume that this point has been proven by clear and convincing evidence, this evidence would not earn TKT a finding of invalidity for lack

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[50] Dr. Kingston testified that the techniques that "are described in the Amgen patents consist of introducing expression vectors that encode exogenous EPO into COS cells or into CHO cells." Trial Tr. at 1321:1-4. Furthermore, Dr. Kingston opined that the Amgen patents do not describe the use of endogenous DNA to produce EPO protein. *Id.* at 1185:4-5; *see also id.* at 1186:6 to 1187:2. Experts called by both parties agreed (though some reluctantly) that the Amgen specification did not explicitly show any examples of human EPO production whereby the endogenous EPO DNA was expressed. *Id.* at 383:23 to 384:19, 1328:4-5, 1329:14 to 1330:1, 2659:11-13.

TKT also points to passages in the specification that tend to suggest that the patent was limited to the use of exogenous DNA: "These polypeptides are also uniquely characterized by being the product of procaryotic or eucaryotic host expression (e.g., by bacterial, yeast and mammalian cells in culture) of exogenous DNA sequences obtained by genomic or cDNA cloning or by gene synthesis." Trial Ex. 1 at 10:15-20. This quotation lends substantial support to TKT's claim, for Amgen seems to be pigeonholing itself by using the terms "uniquely characterized by . . . expression . . . of exogenous DNA sequences . . . ." *Id.* Elsewhere, the patent specification states that "it will be understood that expression of, e.g., monkey origin DNA in monkey host cells in culture and human host cells in culture, actually constitute instances of 'exogenous' DNA expression inasmuch as the EPO DNA whose high level expression is sought would not have its origins in the genome of the host." *Id.* at 37:38-43. Certainly, one would expect the insertion of monkey origin DNA into human host cells in culture to be an instance of exogenous DNA expression because monkey DNA does not originate in the human genome. Yet it is noteworthy that Amgen apparently considered the insertion of monkey origin DNA into monkey host cells in culture as an instance of exogenous DNA expression as well. In order properly to consider such a technique exogenous, the monkey origin DNA would have to be isolated and then reintroduced into a monkey host cell. If, instead, Amgen were able to activate the monkey EPO DNA in the monkey cell, then the specification would presumably have described the technique as endogenous DNA expression. Thus, the implication to be drawn from this statement in the specification is that Amgen did not in fact contemplate applying its techniques to effectuate endogenous DNA expression.

of written description. TKT doctrinally misstates what the written description requirement demands of the patent applicant. When the claim is to a composition rather than a process, the written description requirement does not demand that the specification describe technological developments in the way in which the claimed composition is made that may arise *after* the patent application is filed. *See United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1251 (Fed. Cir. 1989); *In re Koller*, 613 F.2d 819, 824-25 (Fed. Cir. 1980); *see also In re Hogan*, 559 F.2d 595, 606 (Ct. Cust. Pat. App. 1977). Instead, section 112 only requires the Court to determine whether the specification conveys to one of ordinary skill in the art as of 1984 that Dr. Lin invented the *subject matter* claimed in the patents-in-suit. *Reiffin,* 214 F.3d at 1346. The written description inquiry, therefore, focuses on a comparison between the specification and the invention referenced by the terms of the claim—not comparison between how the product was made as disclosed in the patent and future developments of this process that might alter or even improve how the same product is made. Thus, as long as the specification describes the invention referenced by a particular claim, it has met the written description requirement of section 112 even though it utterly fails to describe subsequent technology concerning the manner by which a claimed composition is manufactured.

Claim 1 of the '422 patent claims a product: a pharmaceutical composition. Trial Ex. at 38:39. As a result, whether endogenous or exogenous DNA expression is employed is immaterial and cannot be relied upon as a basis to render Claim 1 of the '422 patent invalid. Because Claim 1 of the '422 patent does not contain any limitations requiring endogenous gene-activation techniques using homologous recombination, the specification need not specifically describe such techniques. Thus, the Court finds that TKT has failed to prove by clear and convincing evidence that Amgen

failed to describe the invention claimed in Claim 1 of the '422 patent such that one of ordinary skill in the art in 1984 would know that Dr. Lin possessed the pharmaceutical composition claimed therein.

b. *'080 Patent*

The Court comes to the same conclusion with respect to Claims 2, 3, and 4 of the '080 patent. Claims 2 and 3 of the '080 patent claim isolated or non-naturally occurring erythropoietin glycoproteins having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of Figure 6. Trial Ex. 3 at 38:39-50. Claim 4 covers pharmaceutical compositions comprising a therapeutically effective amount of the erythropoietin products according to Claims 2 or 3. *Id.* at 38:51-53.

Various passages of the specification describe all of the elements of these claims. The very first sentence of the "Brief Summary" section explains that "[t]he present invention provides, for the first time, novel purified and isolated polypeptide products having part or all of the primary structural conformation (i.e., continuous sequence of amino acid residues) and one or more of the biological properties (e.g., immunological properties and in vivo and in vitro biological activity) of naturally-occurring erythropoietin, including allelic variants thereof." Trial Ex. 1 at 10:9-15; *see also id.* at 10:34-40, 10:50-60. The isolation and purification of expressed polypeptides is also referenced in the "Brief Summary" section as well as in the context of subsequent examples. *Id.* at 11:15-19. In addition, Figure 6 is described extensively in the specification and Figure 6 itself provides critical information regarding the sequence of erythropoietin amino acid residues necessary for the production of claimed EPO glycoproteins. *Id.* at 21:3-19; *see also id.* at 10:50-53. Furthermore, the specification contains complete and detailed

descriptions of the production of isolated and non-naturally occurring human EPO glycoproteins. *See id.* at 23:1 to 24:38 (Example 7); *id.* at 25:29 to 29:7 (Example 10). The patent also disclosed the in vivo biological effect of CHO-produced EPO upon hematocrit levels in mice. *Id.* at 28:13-28. The specification further describes the polypeptide products as:

> suitable for use in erythropoietin therapy procedures practiced on mammals, including humans, to develop any or all of the effects herefore attributed in vivo to EPO, e.g., stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis . . . and, as indicated in Example 10, increasing hematocrit levels in mammals.

Id. at 33:22-30.

Dr. Lodish identified these and other passages within the specification that "to me and to anyone else demonstrated unequivocally [that Dr. Lin] had done what he said he did . . . ." Trial Tr. at 527:11-12. In addition to the relevant portions of column 10 and Examples 7 and 10, Dr. Lodish also opined that "perhaps the most important thing would be the sequence of the EPO gene which he cloned and identified, the sequence of Figure 6 [b]ecause with that sequence in hand one has, as it were, the basic raw materials to use to make EPO as he described in many other ways." *Id.* at 527:19-23. With respect to the gene sequence, Dr. Lodish concluded:

> the gene sequence is an important part of the description because, simply put, with the correct gene sequence in hand, and he certainly had it to demonstrate it, I, as one skilled in the art, or my students or my post-docs, would know that by expressing this in many cells using various promoters one could make that EPO glycoprotein. It

would simply reinforce the other statements in the patent that he actually had it, yes.

Id. at 528:12-19. The Court credits Dr. Lodish's testimony regarding what one skilled in the art would know after reading Dr. Lin's specification regarding the EPO glycoproteins and the pharmaceutical compositions derived therefrom claimed in Claims 2, 3, and 4 of the '080 patent. Thus, after consideration of the documentary and testimonial evidence, the Court finds that TKT has failed to show by clear and convincing evidence that the asserted claims of the '080 patent were not sufficiently described by the specification.

In reaching this conclusion, the Court rejects the same arguments mentioned above that TKT pressed with respect to the '422 patent. In particular, the Court notes that the asserted claims of the '080 patent claim products: polypeptides and pharmaceutical compositions. These product claims are not limited by the processes by which they are made. Thus, the written description requirement does not necessitate that Dr. Lin explicitly describe every possible way in which his EPO polypeptide and pharmaceutical composition could be obtained. Instead, he was merely required to show to those skilled in the art in 1984 that he, in fact, had obtained these products. His specification meets this requirement.

c. *'349 Patent*

The asserted claims of the '349 patent claim recombinant, EPO-producing vertebrate cells and a process for producing erythropoietin comprising the step of culturing these cells under suitable nutrient conditions. Trial Ex. 5 at 38:8-14, 38:18-27, 38:31-36. Because the specification provides sufficient description of the claimed inventions to give notice to one of ordinary skill in the art as of 1984 that Dr. Lin actually possessed the inventions, TKT's written description attack fails here as well.

The specification announces in the "Brief Summary" section that:

> Vertebrate (e.g., COS-1 and CHO) cells provided by the present invention comprise the first cells ever available which can be propagated in vitro continuously and which upon growth in culture are capable of producing in the medium of their growth in excess of 100 U (preferably in excess of 500 U and most preferably in excess of 1,000 to 5,000 U) of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay.

Trial Ex. 1 at 10:4249. Various passages of the specification go on to describe certain aspects of these EPO-producing cells. For example, the specification depicts in Figures 3 and 4 and describes extensively in Examples 6 and 7 the construction of vectors carrying transcription control DNA sequences and EPO DNA. *Id.* at 21:40 to 22:67 (Example 6); *id.* at 23:1 to 24:38 (Example 7). The specification also describes the role of promoter and regulator DNA sequences, *id.* at 2:3-8, and explains that the transcription control DNA sequences "which precede a selected gene (or series of genes) in a functional DNA polymer cooperate to determine whether the transcription (and eventual expression) of a gene will occur," *id.* at 2:10-13. Specifically, the patent identifies its SV40 late promoter as one type of non-human transcription control DNA sequence that an artisan might use to cause the expression of the EPO gene. *Id.* at 24:12-14. Additionally, Example 5 and Figure 6 provide one skilled in the art information regarding the primary structural conformation of human EPO, data which opened the floodgates to high level EPO production.

Furthermore, Example 10 provides a detailed description of the creation of these EPO-producing cells. *Id.* at 25:29 to 29:7. Example 10 instructs skilled artisans to transfect CHO DHFR$^-$ cells growing in media with the vectors earlier

identified in the patent and a mouse DHFR gene. *Id.* at 25:51-59. "Only those cells which have been stably transformed with the DHFR gene, and thereby the EPO gene, survive" when dispersed into media lacking hypoxanthine and thymidine. *Id.* at 25:63-65. The cells can then be propagated continuously in such media. *Id.* at 25:66 to 26:3. The patent then reports the units of human EPO obtained from the culture fluids from the transfected CHO cells. *Id.* at 26:11-18. The specification then describes how a skilled artisan might increase the level of EPO production by employing gene amplification techniques. *Id.* at 26:19-65. Giving rise to claims in the '349 patent that cover cells that produce EPO at specified levels, the specification reports that following gene amplification of the cells, "[t]he effective production rates for these culture conditions were thus 1264 and 2167 $U/10^6$ cells/48 hours." *Id.* at 26:63-65. The combination of these passages in the patent specification describes all of the elements of the asserted claims of the '349 patent.

Though the disclosures themselves provide significant evidence that the claims of the '349 patent are adequately described in the patent, the Court also credits the expert testimony bolstering this conclusion. With respect to Claims 1 and 4 of the '349 patent, Dr. Lodish specifically identified Figures 3, 4, and 6, lines 41 through 49 of column 10, and Examples 7 and 10 as sources of information in the patent that "would inform one of ordinary skill in the art as of 1984 that Dr. Lin possessed the vertebrate cells described" in independent Claims 1 and 4 of the '349 patent. Trial Tr. at 528:23 to 529:22, 530:6 to 531:8. Dr. Wall's testimony corroborates Dr. Lodish's opinion:

> Q. In your opinion, does the Lin patent specification, looking at the claims of the '349 patent, Claims 1 and 4, in particular, the independent claims, in your opinion, does the Lin patent specification describe the subject matter claimed in those claims?

A. Yes, it does.

Q. Where in the patent do you find the description . . . that supports the subject matters that's claimed in the claims of the '349 patent?

A. Vertebrate cells, which are described in Claim 1 and Claim 4, are summarized in Column 10, line 41 through 49. And then specific examples are also provided in Example 7, which refers to COS cell expression, and Example 10, which describes CHO cell expression, and the vectors which you use are those described in Figures 3 and 4 of the patent.

Id. at 2621:9-23; *see also id.* at 2614:7 to 2615:10; Trial Ex. 186(a) Tab 1 at 106. According to these experts, based on the disclosures contained in the patent, one skilled in the art in 1984 would have understood that Dr. Lin possessed vertebrate cells that could be propagated in vitro in culture, comprised non-human transcription control DNA sequences that controlled the transcription of DNA encoding human erythropoietin, and produced human erythropoietin at the levels recited in the claims of the '349 patent. *See id.* at 297:20 to 298:10, 528:23 to 531:8, 533:8 to 534:3, 2613:20 to 2614:6, 2621:9-23. In particular, the specification describes specific examples of cells containing DNA vectors that contain a non-human DNA transcription control sequence, the SV40 viral promoter enhancer, that is functional in vertebrate and mammalian cells. *See id.* at 126:15 to 127:14, 250:6-18, 253:13 to 254:11, 1201:5-8. Furthermore, it was a matter of common knowledge to one of ordinary skill in the art in 1984 that many different transcription control sequences could be used to make the claimed cells. *Id.* at 301:9 to 302:20, 1457:10-24. In light of this testimony and the extensive description contained in the specification, the Court finds that TKT has failed to prove by clear and convincing evidence

that the claims of the '349 patent are invalid for lack of written description.[51]

d. *'933 Patent*

Though the Court has earlier held that the asserted claims of the '933 patent are not infringed, solely for the purpose of providing a more complete record upon review, the Court now addresses whether any of those claims are invalid due to insufficient written description. Upon examination of the evidence, the Court finds that the specification, considered as a whole, fails to convey to one of ordinary skill in the art that Dr. Lin invented the subject matter claimed in the asserted claims of the '933 patent. *See Reiffin*, 214 F.3d at 1346; *see also Vas-Cath*, 935 F.2d at 1563. As a result, the Court finds that TKT has proven by clear and convincing evidence that these claims are invalid for lack of written description.

Claim 1 of the '933 patent claims non-naturally occurring erythropoietin glycoprotein products having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and having glycosylation which differs from that of human urinary erythropoietin. Trial Ex. 2 at 38:17-21. Dependent Claim 2 claims the product meeting the limitations of Claim 1 and requires that such product have a higher molecular weight than human urinary erythropoietin as measured by SDS-PAGE. *Id.* at 38:22-25. Lastly, dependent Claim 9 claims a pharmaceutical composition comprising an effective amount of a glycoprotein product effective for erythropoietin therapy

[51] For the reasons explained with respect to the '422 patent, the Court again rejects not only TKT's argument that Dr. Lin failed adequately to describe human cells that met the additional limitations of the '349 claims, but also TKT's attempt to render the '349 patent invalid on the basis that it fails adequately to describe cells that express the endogenous human EPO gene.

according to Claims 1 or 2 and a pharmaceutically acceptable diluent, adjuvant, or carrier. *Id.* at 39:1-4.

Various portions of the disclosure refer to relevant aspects of these claims. As cited above with respect to the '080 patent, the first sentence of the "Brief Summary" section explains that:

> The present invention provides, for the first time, novel purified and isolated polypeptide products having part or all of the primary structural conformation (i.e., continuous sequence of amino acid residues) and one or more of the biological properties (e.g., immunological properties and in vivo and in vitro biological activity) of naturally-occurring erythropoietin, including allelic variants thereof.

Trial Ex. 1 at 10:9-15; *see also id.* at 10:34-40, 10:50-60. Moreover, Dr. Lin disclosed a complete and detailed explanation of the production of non-naturally occurring human erythropoietin glycoproteins. *Id.* at 23:1 to 24:38 (Example 7); *id.* at 25:29 to 29:7 (Example 10). The patent also provides important data indicating that the glycoproteins have the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells. *Id.* at 28:13-28. Toward the end of the specification, Dr. Lin explained:

> to the extent that polypeptide products of the invention share the in vivo activity of natural EPO isolates they are conspicuously suitable for use in erythropoietin therapy procedures practiced on mammals, including humans, to develop any or all of the effects herefore attributed in vivo to EPO, e.g., stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C

> synthesis . . . and, as indicated in Example 10, increasing hematocrit levels in mammals.

Id. at 33:19-31. Furthermore, with respect to Claim 9, the specification describes nearly all of the limitations of the pharmaceutical composition claimed in the '933 patent. *Id.* at 12:1-7. In particular, Dr. Lin identified specific diluents, adjuvants, and carriers that could be utilized in the delivery of erythropoietin therapy. *Id.* at 33:61 to 34:27. In addition, other sections of the disclosure provide detailed information concerning effective dosages and therapeutic effectiveness. *Id.* at 28:16-27, 33:50-61. These passages provide highly relevant descriptions of nearly all of the limitations of the inventions claimed in the '933 patent. Furthermore, the Court relies upon the testimony of Dr. Lodish, cited above with respect to the glycoproteins claimed in the '080 patent, in finding that, as to each limitation but one, the information contained in the patent conveys to one of ordinary skill in the art that Dr. Lin invented the subject matter claimed in the asserted claims of the '933 patent. *See* Trial Tr. at 527:11-12, 527:19-23, 528:12-19.

Despite these findings favorable to Amgen, TKT persuades the Court by clear and convincing evidence that Dr. Lin's disclosure fails adequately to describe an EPO glycoprotein whose glycosylation differs from that of human urinary erythropoietin, and that this failure is fatal to all three of its asserted '933 claims. Considering the high burden of proof placed upon TKT, the question is admittedly close because Amgen has put on a spirited defense to TKT's charge of invalidity on this point.[52] But, as previously explained in the

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[52] In particular, Amgen (1) directed the Court's attention to numerous sections of the specification that discuss glycosylation and, more precisely, differences in glycosylation from that of human urinary erythropoietin; and (2) elicited testimony from Dr. Cummings concluding that one of ordinary skill in the art as of 1984 would understand that Dr. Lin's invention possessed a non-naturally occurring EPO glycoprotein whose

infringement portion of this opinion, the glycosylation of human urinary erythropoietin is a standardless standard. *See supra* Section IV.E.2, at 139-46. In summary, the documentary and testimonial evidence supporting this conclusion in the infringement context is incorporated here and reveals that (1) the glycosylation of urinary erythropoietin has "enormous heterogeneity"; (2) different purification techniques, several of which were known by one skilled in the art in 1984, result in differing glycosylated erythropoietin populations; (3) despite referring to at least two purification methods, the patent does not identify which human urinary erythropoietin preparation ought be used as a standard, nor would a skilled person know which urinary EPO preparation should be used; and (4) different urinary erythropoietin samples have different glycosylation. As a result, making comparisons between the glycosylation of recombinant EPO and that of human urinary EPO is virtually impossible. This is not to say, however, that such a comparison could not be accomplished as against a *particular* human urinary erythropoietin sample. Instead, the problem lies in the fact that Dr. Lin failed to disclose which of the varying urinary EPO preparations ought be utilized, and contrary to Dr. Cummings' testimony, the Court finds that one of ordinary skill in the art as of 1984 would not be able to guess the appropriate EPO preparation. As a result, the patent fails to convey to one of ordinary skill in the art as of 1984 that Dr. Lin invented an erythropoietin glycoprotein product having glycosylation which differs from that of human urinary erythropoietin. Thus, despite sufficient written description of each of the limitations contained in the three asserted claims of the '933

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glycosylation differed from that of human urinary EPO. *See* Trial Ex. 1 at 5:48-53, 10:28-41, 28:33 to 29:7, Fig.6 (noting asparagine-linked glycosylation by asterisk); Trial Tr. at 569:16-24, 570:20 to 571:2, 607:22 to 614:3, 619:21 to 620:5, 620:13 to 627:12, 653:5 to 654:8, 659:15 to 660:19.

patent save one, if the finding of non-infringement were to be ruled error, this Court would, in the alternative, rule that all three[53] asserted claims of the '933 patent are invalid for lack of written description.[54]

3. *Definiteness*

The Court holds that despite meeting the other limitations of the asserted '933 claims, HMR4396 does not infringe the limitation that the erythropoietin glycoprotein product have "glycosylation which differs from that of human urinary erythropoietin." Nonetheless, the Court now addresses TKT's alternative defense regarding this claim limitation, i.e., that human urinary erythropoietin is indefinite.

According to the relevant statute, "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." 35 U.S.C. § 112. "Determining whether a claim is definite requires an analysis of 'whether one skilled in the art would understand the bounds of the claim when read in light of the specification . . . . If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more.'" *Personalized Media Communications, LLC* v. *Int'l Trade Comm'n*, 161 F.3d 696, 705 (Fed. Cir. 1998) (quoting *Miles Lab., Inc.* v. *Shandon, Inc.*, 997 F.2d 870, 875 [Fed. Cir. 1993]); *see also Space Sys./Loral, Inc.* v. *Lockheed*

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[53] The Court's ruling applies to all three claims because the limitation that the erythropoietin glycoprotein product have glycosylation which differs from that of human urinary erythropoietin is contained in Claim 1 and is required, by dependency, in Claims 2 and 9. Trial Ex. 2 at 38:20-21, 38:23, 39:3.

[54] As should be abundantly clear by this point, in reaching this conclusion, the Court was not persuaded by TKT's alternative arguments that Amgen failed adequately to describe the production of erythropoietin either by use of a human cell line or by activating the otherwise dormant endogenous erythropoietin gene. *See supra* note 51.

Martin Corp., Nos. 99-1255, 99-1289, 2000 WL 1205154, at *10 (Fed. Cir. Aug. 23, 2000) (unpublished opinion); *Amgen, Inc.* v. *Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1217-18 (Fed. Cir. 1991). The focus of the inquiry, then, is on the clarity of the claim terms and the extent to which such terms, viewed from the perspective of one of ordinary skill in the art, sufficiently identify the actual invention. Relating as it does to the Court's performance of its duty to construe the claims, the indefiniteness determination is made as matter of law. *Personalized Media*, 161 F.3d at 705.

As explained in the '933 patent infringement and adequate written description portions of this opinion, *see supra* Section IV.E.2, at 139-46; *supra* Section IV.F.2.d, at 214-16, the term "gylcosylation of human urinary EPO" does not have a precise meaning. Although the language contemplates that a competitor concerned with infringing the '933 patent can empirically determine whether its product's glycosylation differs from the glycosylation of human urinary erythropoietin, a definitive comparison is rendered impossible by the fact that human urinary erythropoietin itself varies significantly. This is not the kind of particular pointing out and distinct claiming that is required by the statute. 35 U.S.C. § 112. Consequently, despite appearing to be "definite," the term actually lacks sufficient clarity to place those of ordinary skill in the art on notice of the bounds of the invention.

Here, the Court incorporates the factual findings, which are summarized above on page 215, *see supra* Section IV.E.2, at 13946; *supra* Section IV.F.2.d, at 214-16, underlying the determination that HMR4396 does not infringe this claim limitation of the '933 patent. As summarized by Drs. Paul T. Matsudaira and Phillips W. Robbins, because different urinary erythropoietin preparations vary in their glycosylation, and because neither the patent nor the prior art provides clear guidance as to which human urinary EPO standard ought be used, one of ordinary skill in the art would be unable to

determine whether a particular erythropoietin has gylcosylation which differs from that of human urinary erythropoietin. Trial Tr. at 1845:13 to 1846:25, 1979:7 to 1980:11, 2314:7-23. The Court relies upon these findings in holding that the term "human urinary erythropoietin" is indefinite. Because the claim term fails to apprise those skilled in the art of the scope of the invention, TKT has proved by clear and convincing evidence that the claim is indefinite, and if upon review, the finding of non-infringement is error, the Court so rules.

4. *Enablement*

At various points throughout this litigation—from the *Markman* hearing right through to the final argument—the Court noted that the issue of enablement would perhaps be the critical area of the contest. Recognizing as much, both parties deployed substantial squadrons to this theater, and the battle raged. After much reflection, the Court finds that Amgen survives, albeit barely.

Like the written description requirement, the statutory basis for the enablement inquiry is section 112, which states:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . . .

35 U.S.C. § 112. The Federal Circuit has elaborated: "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Genentech, Inc.* v. *Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561 [Fed. Cir. 1993]); *see also In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991). The disclosure meets the enablement requirement even if a "rea-

sonable" amount of routine experimentation is necessary in order to practice a claimed invention, as long as such ex perimentation is not "undue." *Enzo Biochem, Inc.* v. *Calgene, Inc.*, 188 F.3d 1362, 1371 (Fed. Cir. 1999); *In re Wands,* 858 F.2d 731, 736-37 (Fed. Cir. 1988). In determining whether the necessary experimentation would be "undue," the Federal Circuit has set forth the following factors to guide the inquiry:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d at 737. Whether claims are sufficiently enabled by the specification is determined as of the filing date of the patent application. *Enzo Biochem*, 188 F.3d at 1371; *Hybritech, Inc.* v. *Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986). Thus, the court makes an enablement determination "retrospectively, i.e., by looking back to the filing date of the patent application and determining whether undue experimentation would have been required to make and use the claimed invention at that time." *Enzo Biochem*, 188 F.3d at 1371-72 (citing *Hybritech*, 802 F.2d at 1384; and *Wright,* 999 F.2d at 1562-63). This determination is made as matter of law, though the legal conclusion rests upon findings of fact. *Nat'l Recovery Tech., Inc.* v. *Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1195 (Fed. Cir. 1999). Moreover, proof of invalidity due to lack of enablement must be clear and convincing, for the presumption of validity includes a presumption that the patent complies with section 112. *See* 35 U.S.C. § 282; *Nat'l Recovery*, 166 F.3d at 1195 (citing *Northern Telecom, Inc.* v. *Datapoint Corp.*, 908 F.2d 931, 941 [Fed. Cir. 1990]). The burden, then, falls squarely upon TKT clearly and con-

vincingly to persuade the Court that Amgen's claims are invalid because they are not enabled.

a. *'422 Patent*

Claim 1 of the '422 patent claims a pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin, which is purified from mammalian cells grown in culture, and a pharmaceutically acceptable diluent, adjuvant or carrier. Trial Ex. 6 at 38:37-41. In light of the legal framework, the Court's duty is to determine whether the specification of Dr. Lin's patents teaches those skilled in the art how to make and use the full scope of the claimed pharmaceutical composition without undue experimentation. *Enzo Biochem*, 188 F.3d at 1371-72.

First, to the extent that such findings are relevant here, the Court incorporates the numerous factual findings regarding the sufficiency of Dr. Lin's disclosure that undergird the Court's finding that Claim 1 of the '422 patent is not invalid due to inadequate written description. *See supra* Section IV.F.2.a, at 203-07. Dr. Lin's disclosure provides ample information teaching those skilled in the art how to manipulate certain cells genetically so that they produce human erythropoietin. *See, e.g.*, Trial Ex. 1 at 25:29 to 29:7 (Example 10); *id.* at Fig.6; Trial Tr. at 125:13-24. In addition, though the Court notes that many purification techniques were already well-known in the art as of 1984, *see* Trial Exs. 42, 2012, 2233, 2235-36, 2247, 2252, 2333, 2440; Trial Tr. at 632:13 to 634:1, 1846:19-22, 1970:6 to 1979:8, 2189:16 to 2190:25, 2193:9 to 2194:15, 2197:2-19, the specification described how to purify human erythropoietin from certain mammalian cells grown in culture. Trial Ex. 1 at 11:15-19, 28:28-32; Trial Tr. at 1631:21 to 1632:6, 1982:24 to 1983:17. The specification also teaches skilled artisans how to prepare and use pharmaceutical compositions containing therapeutically effective amounts of human erythropoietin. Trial Ex. 1 at 12:1-7, 33:50 to 34:27; Trial Tr. at 125:13-24, 137:5-

11, 264:4 to 265:24, 1336:18-20. Thus, at least with respect to the limitations of Claim 1 concerning both the purification and the therapeutically effective use of the erythropoietin product, between what those skilled in the art already knew and what Dr. Lin disclosed to the world in the specification, a skilled artisan would be enabled to make and use the claimed pharmaceutical composition. The question remains, however, whether the specification enables one of ordinary skill in the art to practice the invention using *all* cultured mammalian cells—this is the scope of the claim. Put differently, in light of the breadth of the disclosure, should Amgen's claims have been limited to a smaller subset of cell types?

Dr. Lin's disclosure provides only two examples of mammalian cells that produce erythropoietin. Trial Ex. 1 at 23:1 to 24:38 (Example 7, using COS-1 cells); *id.* at 25:29 to 29:7 (Example 10, using CHO cells). The question then arises whether the explicit disclosure of just two mammalian cell lines warrants a claim covering all mammalian cells. Rather than properly seeking a claim equal in measure to the scope of the disclosure, it appears that Dr. Lin claimed far more than what he delivered. This is exactly the type of conduct that the enablement requirement is intended to smoke out. But a claim should not be squeezed uncomfortably into the dinghy of a particular example, if the teachings of the patent warrant the capacious comfort of an ocean liner. TKT, of course, argues that the teachings simply are not so broad.

True, Drs. Lodish and Wall testified that one of ordinary skill in the art in 1984 could have practiced the Lin inventions in a variety of different mammalian cell types with routine experimentation. Trial Tr. at 137:21 to 142:1, 251:6 to 253:9, 2605:9 to 2606:1, 2608:19 to 2609:16; 2674:8 to 2676:6, 2677:24 to 2678:25. As already mentioned with respect to the written description requirement, Dr. Lodish explained that Example 10 "teaches that one can use vertebrate cells, mammalian cells in this process," *id.* at 140:6-7, and that

"[o]ne of ordinary skill in the art, me, my students, would have understood this not to be limited to the specific types of cells that we[re] used in this example, that other vertebrate cells, mammalian cells, could have been used," *id.* at 140:7-11. *See also id.* at 251:3-12 (discussing additional sections of the specification).[55] He then confidently added that the "techniques described in the Lin patent are equally applicable to [mammalian] cells, other than COS or CHO cells, without question." *Id.* at 251:18-20. During an exchange with the Court, Dr. Lodish elaborated on his reasoning. He explained that one of ordinary skill in the art would infer from the examples using COS-1 and CHO cells that similar outcomes could be expected from other mammalian cells "[b]ecause these cells, vertebrate cells, mammalian cells specifically, make proteins and process them in substantially the same way." *Id.* at 141:16-18. All mammalian cells produce and secrete hormones like EPO by means of the same fundamental process of gene transcription, RNA splicing, mRNA translation, and post-translational modification. *Id.* at 83:6 to 88:13, 120:9-22, 141:15-20; *see also id.* at 2550:7-15, 2580:18-22. Dr. Lodish did admit that "there may be minor differences, but those would be easy to figure out experimentally." *Id.* at 141:19-20. Thus, "with a strong likelihood of success, one could have used cells other than the CHO cells or the COS cells that [Lin] used in this patent." *Id.* at 141:20-23; *see also id.* at 542:25 to 543:7, 2605:9 to 2606:1. Furthermore, there is no evidence in the record indicating that human cells are somehow different from other mammalian cells and would, therefore, be unsuitable for producing erythropoietin following Dr. Lin's teachings. *Id.* at

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[55] The Court also notes that by 1984, a variety of mammalian cells useful for protein expression had been adapted for growth in culture and were readily available to those of ordinary skill in the art from the American Type Culture Collection ("ATCC"). Trial Tr. at 2678:17 to 2679:5, 2685:24 to 2686:19. A number of cultured human cell lines were available as well. *Id.* at 252:19 to 253:3, 1209:19-21, 2616:2-12.

2556:5-13. Consistent with Dr. Lodish's testimony, Dr. Wall testified that the "teachings of the Lin patent describe vertebrate mammalian cells, and the techniques are all applicable to human cells which can be grown in culture." *Id.* at 2623:2225. When pressed regarding the difficulty of identifying suitable expression systems for making erythropoietin, for instance, Dr. Wall and his interrogator had the following exchange:

> Q. [Y]ou would have to determine whether . . . there were suitable expression systems for making EPO in those cells? Is that correct?
>
> A. [Y]ou wouldn't need to design an expression system, that there were already available broadly active, that is, with a broad spectra of host cell specificity or activity many suitable vectors.
>
> Q. And you need to find out whether the particular host cell you were looking at possessed a suitable system, correct?
>
> A. It would be a routine experiment to test one of the readily available SV40 or mouse metallothionein or whatever other expression system you wanted to try.

Id. at 2674:19 to 2675:9. Throughout the testimony of these witnesses, a theme becomes apparent: any challenge which one of ordinary skill in 1984 might have encountered in attempting to make and use the claimed invention using other cultured mammalian cells could be resolved by experimentation falling short of "undue." As the Court finds this testimony credible, it cannot find by clear and convincing evidence that after reasonable experimentation one skilled in the art as of 1984 would not have been able to make and use a pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin purified from mammalian cells grown in culture.

Another issue merits consideration, however. Throughout this litigation, TKT has made every effort to point out the fact

that whereas Amgen recombines exogenous EPO DNA sequences, TKT activates the endogenous EPO gene. As previously mentioned, TKT attempted to insert an exogenous DNA limitation somewhere within nearly every asserted claim. Then and now, the Court maintained that the claim language could not reasonably be read to incorporate such a limitation. Instead, the Court opined that if the exogenous-endogenous dispute belonged anywhere in this case, it ought be faced in the context of the validity arguments. Well, here it is.

As an initial matter, TKT's contention must be clarified. Taking the Court's claim construction as issued, TKT notes (as it must) that the claimed pharmaceutical composition is not defined by the EPO gene's relationship to its host. Having lost that battle during the *Markman* hearing, TKT now comes about and argues, essentially, that "if the claim construction is that broad, then Amgen's disclosure better meet it." Fair enough.

TKT is correct that HMR4396 Injection is produced by activating the endogenous EPO gene and that, in contrast, all of Dr. Lin's specific examples are devoted to the insertion of exogenous EPO DNA into host cells. As earlier detailed with respect to the written description analysis of the '422 patent, TKT's evidence tends to show that Amgen's invention was limited to the expression of exogenous DNA. *See supra* note 50. While the Court is willing to assume that this contention has been proven by clear and convincing evidence, a finding of invalidity for lack of enablement does not follow. Like the written description requirement, *see supra* Section IV.F.2.a, at 200-03, where the method is immaterial to the claim, the enablement inquiry simply does not require the specification to describe technological developments concerning the method by which a patented composition is made that may arise after the patent application is filed. *See United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247,

1251 (Fed. Cir. 1989); *In re Koller*, 613 F.2d 819, 824-25 (Ct. Cust. Pat. App. 1980); *see also In re Hogan*, 559 F.2d 595, 606 (Ct. Cust. Pat. App. 1977). Moreover, the law makes clear that the specification need teach only one mode of making and using a claimed composition. *See Johns Hopkins Univ.* v. *Cellpro, Inc.*, 152 F.3d 1342, 1361 (Fed. Cir. 1998); *Engel Indus. Inc.* v. *Lockformer Co.*, 946 F.2d 1528, 1533 (Fed. Cir. 1991). As a result, contrary to what TKT proposes here, there is no requirement that the specification enable every mode for making and using the claimed products.[56] Thus, the facts that (1) TKT makes the same pharmaceutical composition but by a different method; and (2) that such method is not taught in the Amgen patent, are wholly immaterial. As a result, because the record is replete with persuasive evidence that Dr. Lin's disclosure taught those skilled in the art at least one method of making and using the pharmaceutical composition of Claim 1 of the '422 patent, the specification is sufficient to overcome this enablement challenge.

b. *'080 patent*

Claims 2 and 3 of the '080 patent claim erythropoietin glycoproteins having certain characteristics, and Claim 4 claims a pharmaceutical composition comprising a therapeutically effective amount of the erythropoietin products according to Claim 2 or 3. Trial Ex. 3 at 38:39-53. Dr. Lin's

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[56] The reason for such a rule is clear. What would be the value in patenting a composition at all if, by making the slightest alteration in the method of making what is nonetheless the same product, a competitor were able to evade liability? A patent system that permitted such conduct would remove the carrot dangling in front of the inventor's nose. If inventors were so easily divested of their limited monopoly rights attendant to their novel, useful, and nonobvious contributions, they would likely abandon their pursuits and thereby inhibit progress. The law does not permit such an outcome.

disclosure enables those skilled in the art as of 1984 to practice these inventions.

In reaching this conclusion, the Court incorporates within its analysis the evidentiary foundation relied upon to find that the '080 claims did not run afoul of the written description requirement. *See supra* Section IV.F.2.b, at 203-07. In summary, the text and figures of the specification describe the isolation and purification of the claimed erythropoietin polypeptides in such a manner as to enable one skilled in the art to make and use these polypeptides as well as pharmaceutical compositions containing them. *See, e.g.*, Trial Ex. 1 at 10:9-15, 10:34-40, 10:50-60, 11:15-19, 21:3-19, 23:1 to 24:38 (Example 7), 25:29 to 29:7 (Example 10), 31:13-54, 32:44-60, 33:19-30, 35:10-17, Fig.6; Trial Tr. at 527:19-23, 528:12-19. Even Dr. Kingston, who was called by TKT, agreed that if one of ordinary skill in the art as of 1984 followed Example 10, then such person would be able to make an erythropoietin polypeptide in CHO cells. Trial Tr. at 2110:6-10. Neither he, nor any other witness, claimed that the specification's examples were inoperable. *Id.* at 2109:20-25. Furthermore, to the extent that a skilled artisan would be led astray by the erroneous Hexose value or the additional arginine at position 166 of the deduced amino acid chain displayed in Figure 6, both discrepancies were discoverable through reasonable experimentation. As a result, these scientific errors do not render any of the asserted claims invalid for lack of enablement.

TKT argues that the asserted '080 patent claims are invalid because the Lin patent specification does not enable one skilled in the art to produce erythropoietin glycoproteins (and pharmaceutical compositions) by activating the endogenous EPO gene in a human cell. As previously explained, however, this unique method by which TKT achieves the same outcome need not be enabled provided that the patentee teaches a skilled artisan at least one method of obtaining a

claimed composition. *See supra* Section IV.F.4.a, at 228-30. Furthermore, whereas the scope of Claim 1 of the '422 patent, which recites "mammalian cells," reaches a broad range of host cells capable of expressing the human EPO gene, the asserted claims of the '080 patent do not. Thus, TKT's argument that the specification fails to enable the production of EPO using cells other than CHO cells (including human cells) is inapposite. Thus, the Court finds that one of ordinary skill in the art would have been able to make and use the claimed erythropoietin glycoproteins and the pharmaceutical composition containing them.

c. *'349 Patent*

As to the asserted claims of the '349 patent, the Court also concludes that the written description, when combined with the knowledge of those of ordinary skill in the art as of 1984, teaches skilled artisans how to make and use the claimed unique vertebrate cells. In analyzing TKT's written description challenges to the '349 patent, the Court considered various passages from the specification as well as helpful testimony from the witnesses. Much the same evidence undergirds the Court's enablement holding. *See supra* Section IV.F.2.c, at 207-11.

In sum, various passages of the specification provide important data regarding, for instance, promoter and regulator DNA sequences, the creation of vectors carrying transcription control DNA sequences and human EPO DNA, the primary structural conformation of human EPO, selection and amplification techniques, and methods to quantify the erythropoietin production rates of the cells. *See, e.g.*, Trial Ex. 1 at 2:3-8, 2:10-13, 10:42-49, 21:40 to 22:67 (Example 6), 23:1 to 24:38 (Example 7), 25:29 to 29:7 (Example 10), Fig.6. Moreover, the art was already rich in certain aspects of these teachings. For example, as of 1984, ordinary skilled artisans had identified a variety of promoters that could be used to promote gene expression in a variety of mammalian and

vertebrate cells. Trial Tr. at 301:12 to 302:4, 302:23 to 303:2. Determining whether a given promoter would operate within a particular cell type was a matter of routine experimentation. *Id.* at 302:5-20. One skilled in the art at that time also would have understood that a variety of vertebrate cells adapted for growth in culture could be obtained from the ATCC. *Id.* at 2678:17 to 2679:5, 2685:24 to 2686:19. In addition, a number of cultured human cell lines were available. *Id.* at 252:19 to 253:3, 1209:19-21, 2626:2-12. One skilled in the art of molecular biology would have understood that because all vertebrate cells produce and secrete hormones by the same fundamental processes, the teachings displayed in the '349 patent were readily applicable to the entire range of cultured vertebrate cells, including human cells. *Id.* at 83:6 to 88:13, 120:9-22, 141:15-20, 2550:7-15, 2556:5-13, 2580:18-22. These aspects relating to the Lin patents were already well known in the art prior to Dr. Lin's disclosure.

Building on this art, Dr. Lin's disclosure taught ordinary skilled artisans how to practice the claimed vertebrate cell inventions. *Id.* at 254:12 to 255:23. In particular, the teachings enabled one of ordinary skill in the art to use various cultured vertebrate and mammalian cells, including human cells, to produce human EPO. *Id.* at 123:12-22, 137:21 to 138:1, 140:6 to 142:1, 250:3 to 253:12, 541:15 to 543:10, 627:21 to 629:4, 1112:16 to 1113:11, 1124:23 to 1125:2, 2109:20 to 2110:21, 2554:21 to 2555:3, 2556:11-13, 2580:11-25. With the assistance of the Amgen specification, a skilled artisan would have been able to determine with routine experimentation which cultured vertebrate cells would produce human EPO. *See id.* at 137:21 to 138:12, 139:8-20, 140:6 to 142:1, 534:10 to 536:9, 2679:17 to 2679:5, 2685:24 to 2686:19. The same is true with respect to whether certain of the various promoters could be operatively linked to control the transcription of the DNA encoding human EPO. *See id.* at 514:22 to 515:5. The specification teaches how to use cultured vertebrate cells to make cells that contain non-

human DNA sequences that control transcription of human EPO DNA and, upon growth in culture, are capable of producing EPO at the levels recited in the claims. *Id.* at 254:1-23, 2605:9-20, 2605:22 to 2606:1. Among the many techniques described in the '349 patent for obtaining such cells are the use of (1) strong non-human promoters and enhancers; (2) selectable markers for isolation of cells capable of stable EPO expression in culture; (3) amplified markers for selection of cells containing amplified copies of EPO DNA under the control of non-human transcription control sequences; and (4) cell cloning. *Id.* at 2581:15 to 2582:3, 2599:15 to 2600:18, 2601:18 to 2603:25, 2604:13 to 2605:1. The patent also enables one of ordinary skill in the art to isolate EPO from EPO-producing cells and to measure such EPO. *Id.* at 378:12-23.

The extent of the enabling disclosure is also demonstrated by a series of post-filing publications that describe the creation of EPO-producing cultured human, monkey, and hamster cells using the techniques taught in the Amgen specification. *See Gould* v. *Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987) (explaining that an expert may rely upon post-filing publications that apply known techniques as of the filing date to show that the specification was enabling). Yanagi, for example, applied the teachings of the '349 patent to make cultured human cells capable of producing the claimed amounts of human EPO. *See* Trial Ex. 43; Trial Tr. at 2104:2-8, 2105:8-19, 2606:2 to 2607:13, 2608:7-13. Powell, similarly, made $DHFR^+$, COS, and BHK (baby hamster kidney) cells containing amplified human EPO DNA under the control of non-human transcription control sequences that were capable of producing human EPO at the levels recited in the '349 claims. *See* Trial Ex. 2323; Trial Tr. at 2609:11-16, 2609:24 to 2610:25. Ohashi, meanwhile, made EPO-producing $DHFR^+$ human cells that contained amplified human EPO DNA under the control of non-human transcription control sequences. Trial Tr. at 2612:20 to 2613:17. The fact that these re-

searchers were capable of making EPO-producing cells using non-human transcription control sequences and either amplified or non-amplified EPO DNA in various types of cultured cells including human cells further suggests that Amgen's specification was enabling. *Id.* at 2607:19 to 2608:1, 2608:19 to 2609:1.

The Court also notes that TKT failed to prove—at least by clear and convincing evidence—that one of ordinary skill in 1984 would not have been able to make and use vertebrate cells having the properties of Dr. Lin's claimed cells without undue experimentation. More precisely, TKT has failed to provide clear and convincing evidence that any person was unable to make and use the inventions claimed in the '349 patent in any vertebrate cell. In fact, Dr. Kingston, TKT's expert, conceded that a post-doctoral fellow working in his laboratory in 1984, applying the techniques described in the '349 patent, would have been able to make cultured human cells capable of expressing human EPO. *Id.* at 2111:13 to 2112:4, 2113:6-16.

TKT points to a portion of the prosecution history of the '349 patent in order to support its non-enablement contentions. During the prosecution of the '349 patent claims, Examiner Martinell rejected certain claims under 35 U.S.C. § 112 and stated that "[t]he instant application teaches and enables only cells that have been transformed with exogenous DNA that encodes erythropoietin (EPO) that have the high EPO production required by the claims." Trial Ex. 5 Tab 10 at 204. Although TKT argues that this snippet limits Amgen's cell claims to cells that have been transfected with exogenous EPO DNA, read in context, it does not support TKT's argument. The claim to which Examiner Martinell referred in the rejection was then pending Claim 42: "Vertebrate cells which can be propagated in vitro and which upon growth in culture are capable of producing in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in

48 hours as determined by radioimmunoassay." *Id.* at 171. Thus, rejected Claim 42 literally encompassed vertebrate cells that had not been genetically manipulated at all—with endogenous *or* exogenous DNA—but were nonetheless capable of producing the recited levels of human EPO. In light of the originally filed claim, one must examine not only TKT's oft-quoted sentence of the rejection but also the statement that followed it: "[t]he instant application does not guide one of skill in the art in the discovery of *non-transformed vertebrate cells* that are capable of the high EPO production recited in the instant claims." *Id.* at 204 (emphasis added). Moreover, in support of his rejection, Examiner Martinell cited three publications, all of which described human cells that had not been genetically manipulated that produced EPO at levels far below the levels recited in the claims. *See id.* In light of this additional sentence and the cited publications, it becomes clear that Examiner Martinell was not concerned about limiting the claims so that genetic manipulation was endogenous rather than exogenous; rather, he was concerned about limiting the cell claims generally to transformed, or genetically manipulated, rather than non-transformed vertebrate cells. This conclusion is solidified by Amgen's submitted amended claims which, rather than limiting the claimed invention to cells comprising exogenous DNA encoding human EPO, limited the cell claims by adding limitations concerning genetic manipulation. In particular, the amended claims, which were later issued as Claims 1 and 4 of the '349 patent, were limited to vertebrate cells "comprising non-human DNA sequences that control transcription of DNA encoding human erythropoietin" or "which comprise transcription control DNA sequences, other than human erythropoietin transcription control sequences," respectively. *Id.* at 235, 242. Examiner Martinell agreed that the amended claims overcame his enablement rejection and consequently withdrew the section 112 rejection and allowed the amended claims to issue. *Id.* at 235, 255. It stands to reason that if he were objecting on the

basis that the Lin patents only enabled the manufacture of EPO-producing cells by using exogenous EPO DNA, then the enablement rejection would not have been withdrawn. Thus, the Court is not persuaded by clear and convincing evidence that Amgen's specification fails to enable ordinary skilled artisans to make vertebrate cells meeting all of the limitations of the '349 patent claims.[57]

TKT also points to Amgen's human '293 cell experiments as evidence that the '349 patent is not enabling. *See generally* Trial Ex. 2092 (Laboratory Notebook issued to J. Egrie). TKT contends that Dr. Lin should not have claimed classes of EPO-producing cells as broad as "mammalian" or "vertebrate" because these human '293 cell experiments failed to produce EPO in sufficient amounts.

The Court agrees that these experiments demonstrate levels of EPO production falling far short of the magnitude encompassed by the '349 claims. Moreover, the Court agrees that these experiments strongly suggest that such high level expression could not be obtained from this human cell line, at least by means of techniques known to those skilled in the art in 1984.

The '293 experiments, however, occurred months before Dr. Lin first disclosed his vertebrate cell inventions in the '349 patent. More importantly, as indicated above, *see supra* Section IV.F.1.c, at 189-90, the '293 experiments were not performed for the purpose of yielding high levels of EPO expression, Trial Tr. at 2556:13-16. Instead, they were transient expression experiments designed to achieve fast but

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[57] Because Amgen is only required to enable skilled artisans to make its claimed product by one method, the Court again rejects TKT's argument that the '349 patent claims are invalid because they fail to enable one of ordinary skill in the art to manufacture cells capable of expressing EPO from endogenous EPO DNA. *See supra* Section IV.F.4.a, at 227-30.

short-term expression of the EPO gene sequence cloned by Dr. Lin rather than stable transformants capable of high level EPO production. *Id.* at 428:10 to 429:12, 967:3-18, 1112:16 to 1113:11, 2111:19 to 2112:4, 2556:25 to 2557:8, 2559:1-6, 2568:9 to 2569:8, 2572:22 to 2573:4. Specifically, these experiments were designed to confirm that Dr. Lin had cloned an intact, complete DNA sequence encoding human EPO, *see id.* at 2568:11-23, and they did not employ the various techniques later described in Example 10 to increase EPO production levels. The '293 experiments, for example, did not include the use of (1) a strong promoter; (2) a selectable marker to allow selection of stable transformants; (3) an amplifiable marker to allow amplification of the EPO DNA; and (4) the use of sub-cloning to isolate homogeneous populations of high producing cell clones. *Id.* at 2569:16 to 2572:21, 2575:15 to 2577:23. Thus, while it appears that Amgen failed to obtain high level EPO expression in a human cell line, which directly challenges the patent's scope of enablement, Amgen was not attempting to apply all of the teachings of the '349 patent in those experiments. As a result, while the '293 experiments prove more likely than not that Amgen's '349 patents are not enabled, this Court does not find such proof clear and convincing.

d. *'933 Patent*

Although the Court has found that HMR4396 does not infringe the asserted claims of the '933 patent, the Court here addresses whether any of those three claims survive TKT's enablement onslaught. Claim 1 of the '933 patent covers non-naturally occurring erythropoietin glycoprotein products having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and having glycosylation which differs from that of human urinary erythropoietin. Trial Ex. 2 at 38:17-21. Dependent Claim 2 also requires that such product have a higher molecular weight than human urinary erythropoietin as

measured by SDS-PAGE. *Id.* at 38:22-25. Dependent Claim 9, meanwhile, covers pharmaceutical compositions comprising an effective amount of a glycoprotein product effective for erythropoietin therapy according to Claims 1 or 2 and a pharmaceutically acceptable diluent, adjuvant, or carrier. *Id.* at 39:1-4. The limitations contained in these claims are widely described throughout the specification, as is apparent from the extensive evidence cited by the Court with respect to the sufficiency of the written description of the '933 patent. *See supra* Section IV.F.2.d, at 211-16. For example, the specification discusses novel purified and isolated polypeptide products having part or all of the primary structural conformation and one or more of the biological properties of naturally-occurring erythropoietin, and provides a detailed explanation of the production of such erythropoietin glycoprotein products. Trial Ex. 1 at 10:9-15, 10:34-40, 10:50-60, 23:1 to 24:38 (Example 7), 25:29 to 29:7 (Example 10). In conjunction with disclosures concerning in vivo biological activity, therapeutic effectiveness, and other aspects of the '933 claims, these passages nearly enable one of ordinary skill in the art to practice the inventions claimed in the '933 patent. *Id.* at 12:17, 28:13-28, 33:19-31, 33:50 to 34:27; Trial Tr. at 625:11 to 629:11, 656:2 to 661:4.

Despite these enabling disclosures, Dr. Lin's specification falters, which by this point should come as no surprise to the reader, because it fails to enable one of ordinary skill in the art to compare the glycoyslation of the recombinant EPO product with that of human urinary erythropoietin. The Court directs the reader to more extensive discussions of this matter contained in the infringement, *see supra* Section IV.E.2, at 139-46, adequate written description, *see supra* Section IV.F.2.d, at 214-16, and definiteness, *see supra* Section IV.F.3, at 218-19, portions of this opinion. Consequently, an ordinary skilled worker would be unable to perform the experimental analysis necessary to confirm whether the manufactured glycoprotein product has glycosylation which

differs from that of human urinary erythropoietin. The Court therefore concludes, should the finding of non-infringement prove erroneous, that TKT has proven by clear and convincing evidence that the '933 patent specification does not enable one of ordinary skill in the art to make and use the erythropoietin glycoprotein product (and related pharmaceutical composition) encompassed within the three asserted claims of the '933 patent.

V. CONCLUSION, DECLARATION, AND ORDER FOR JUDGMENT

As this opinion comes to its conclusion, it is appropriate to reiterate that it truly has been an honor to have presided over a case litigated with such skill, intelligence, and integrity. The attorneys representing both parties have done an extraordinary job in teaching the Court many of the nuances of both this challenging area of law and this rather complicated realm of science. Litigation, however, is a rather rough-edged zero-sum enterprise. Accordingly—

For the reasons set forth above, the Court declares:

> Claims 1, 2, and 9 of the '933 patent are not infringed, and, if this finding is error, those claims are invalid for lack of an adequate written description, indefiniteness, and lack of enablement.
>
> Claims 4 through 9 of the '698 patent are not infringed.
>
> Claims 2 through 4 of the '080 are valid, enforceable, and infringed under the doctrine of equivalents.
>
> Claims 1, 3, 4, and 6 of the '349 patent are valid, enforceable, and literally infringed, whereas Claim 7 of the same patent is not infringed.
>
> Claim 1 of the '422 patent is valid, enforceable, and literally infringed.

An appendix follows, setting forth the Court's holding in tabular form.

Judgment will enter so declaring.

/s/ William G. Young
WILLIAM G. YOUNG
CHIEF JUDGE

APPENDIX[58]

	'933 Patent			'698 Patent	'080 Patent	'349 Patent					'422 Patent
	Claim 1	Claim 2	Claim 9	Claims 4-9	Claims 2-4	Claim 1	Claim 3	Claim 4	Claim 6	Claim 7	Claim 1
Literally Infringed?	no	no	no	no	no	yes	yes	yes	yes	no	yes[59]
Infringed by Doctrine of Equivalents?	no	no	no	no	yes		yes[60]		yes[60]	no	
Anticipated?	no	no	no		no	no	no	no	no		no
Obvious?	no	no	no		no	no	no	no	no		no
Inequitable Conduct?	no	no	no		no	no	no	no	no		no
Adequate Written Description?	no[63]	no[63]	no[63]		yes	yes	yes	yes	yes		yes
Definite?	no[60]	no[63]	no[60]								
Enabled?	no[60]	no[63]	no[60]		yes	yes[61]	yes[61]	yes[61]	yes[61]		yes
Final Result	not infringed	not infringed	not infringed	not infringed	valid and infringed	valid and infringed	valid and infringed	valid and infringed	valid and infringed	not infringed	valid and infringed

[58]Where an issue is left blank, it has been rendered moot by the infringement analysis or has not been raised by the parties.

[59]Ruling on summary judgment record.

[60]Dicta.

[61]Albeit barely.

APPENDIX F

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

05-1157

AMGEN INC.,
Plaintiff-Appellee,

v.

HOECHST MARION ROUSSEL, INC.
(now known as Aventis Pharmaceuticals Inc.)
and TRANSKARYOTIC THERAPIES, INC.,
Defendants-Appellants.

ON PETITION FOR PANEL REHEARING
AND REHEARING EN BANC

Before MICHEL, *Chief Judge*, NEWMAN, MAYER, LOURIE, *Circuit Judges*, CLEVENGER, *Senior Circuit Judge*,* RADER, SCHALL, BRYSON, GAJARSA, LINN, DYK, PROST, and MOORE, *Circuit Judges*.

ORDER

A combined petition for panel rehearing and rehearing en banc was filed by the Appellee, and a response thereto was invited by the court and filed by the Appellants. The petition for rehearing was referred to the panel that heard the appeal, and thereafter the petition for rehearing en banc and response were referred to the circuit judges who are authorized to request a poll whether to rehear the appeal en banc. A poll

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* Senior Judge Clevenger, who was on the original panel, participated only in decision on the petition for panel rehearing.

was requested, taken, and failed.

Upon consideration thereof,

IT IS ORDERED THAT:

(1) The petition for panel rehearing is denied.

(2) The petition for rehearing en banc is denied.

(3) The mandate of the court will issue on November 29, 2006.

MICHEL, *Chief Judge*, with whom RADER, Circuit Judge, joins, dissents in the denial of the petition for rehearing en banc in a separate opinion.

NEWMAN, *Circuit Judge*, dissents in the denial of the petition for rehearing en banc in a separate opinion.

LOURIE, *Circuit Judge*, concurs in the denial of the petition for rehearing en banc in a separate opinion.

RADER, *Circuit Judge*, dissents in the denial of the petition for rehearing en banc in a separate opinion.

GAJARSA, *Circuit Judge*, with whom LINN, and DYK, *Circuit Judges*, join, concur in the denial of the petition for rehearing en banc in a separate opinion.

MOORE, *Circuit Judge*, dissents in the denial of the petition for rehearing en banc in a separate opinion.

FOR THE COURT

Date

Jan Horbaly
Clerk

cc: Lloyd R. Day, Jr., Esq.
Carter G. Phillips, Esq.

November 22, 2006

MICHEL, *Chief Judge*, and RADER, *Circuit Judge*, dissenting from the denial of the petition for rehearing en banc.

Rehearing this case en banc would have enabled us to reconsider *Cybor*'s rule of de novo review for claim construction in light of our eight years of experience with its application. I have come to believe that reconsideration is appropriate and revision may be advisable.

In my view, four practical problems have emerged under the *Markman-Cybor* regime: (1) a steadily high reversal rate; (2) a lack of predictability about appellate outcomes, which may confound trial judges and discourage settlements; (3) loss of the comparative advantage often enjoyed by the district judges who heard or read all of the evidence and may have spent more time on the claim constructions than we ever could on appeal; and (4) inundation of our court with the minutia of construing numerous disputed claim terms (in multiple claims and patents) in nearly every patent case.

Our standard of review of no deference to the trial judge's claim constructions, expressed in *Cybor*, rests upon the premise that claim construction is always a purely legal exercise, devoid of factual content. We have likened claim construction to statutory construction. I believe that this analogy is open to serious question. In interpreting statutes, a judge, whether trial or appellate, essentially asks himself/herself, "What does the disputed term mean to me, the judge, as an artisan in the law?" With claim construction, on the other hand, the judge is supposed to inquire, essentially, "How would the average artisan in the relevant field of technology understand the disputed claim terms in the context of the rest of the patent, the prosecution history, and the prior art?"

It seems to me that the claim construction question often cannot be answered without assessing, at least implicitly,

what the average artisan knew and how she thought about the particular technology when the patent claims were written. To make such determinations, the trial judge necessarily relies upon prior art documents and other evidence concerning the skill of the ordinary artisan at the relevant time. Indeed, trial judges are arguably better equipped than appellate judges to make these factual determinations, especially in close cases. In such instances, perhaps we should routinely give at least some deference to the trial court, given its greater knowledge of the facts. Or, perhaps other adjustments to our current practice should be considered.

Whatever our resolution, however, I believe the time has come for us to re-examine *Cybor*'s no deference rule. I hope that we will do so at our next opportunity, and I expect we will.

NEWMAN, *Circuit Judge*, dissenting from denial of the petition for rehearing *en banc*.

The issue for rehearing *en banc* is the Federal Circuit's rejection of the district court's construction of the claim term "a therapeutically effective amount." My concern is with this court's methodology and rationale of claim construction, and with the sources on which the panel majority relied (or failed to rely) in arriving at its changed claim construction. The district court had correctly applied this court's precedent, requiring affirmance.

I

In brief, the panel majority construed the claims more broadly than the invention that was patented; thus the court ignored the patentee's purpose of writing claims that avoid the prior art — a purpose essential to every claim in every patent — by now construing the claims so that, as the panel majority recognized, they may read on the prior art. The patentee's purpose of including the critical limitation to "a therapeutically effective amount" of the genetically engineered erythropoietin (EPO) was to distinguish the prior art EPO isolates, which were not therapeutically effective to "heal or cure," in the district court's words. Thus this court's claim construction diverges from the specification and the prosecution history, and presents a claim construction that impinges on the prior art and thereby fosters invalidity. From this analytic method of claim construction and the denial of rehearing *en banc* I must, respectfully, dissent.

The methodology of claim construction that the court has here adopted raises issues that were laid to rest in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005), where the *en banc* court disavowed the view that a patent claim can be construed more broadly than the invention to which it gives legal effect. In *Phillips* that unwarranted breadth was found in claim construction based on general dictionary definitions of

claim terms, rather than relying on the specific technical usage in the specification; in this case the unwarranted breadth is found in the court's claim construction that may embrace the prior art, despite the exclusion of that subject matter by the prosecution history.

The district court, construing the claims in light of the specification and the prosecution history, construed "a therapeutically effective amount" as "a quantity that produces a result that in and of itself helps to heal or cure." That construction was the basis on which the patentee distinguished its genetically engineered EPO from the chemically identical EPO in known isolates of naturally occurring EPO, for the prior art product contained insufficient EPO to heal or cure. Thus the claim limitation to "a therapeutically effective amount" of EPO was critical to allowance. During an extensive prosecution, the applicant stated that

> naturally occurring human erythropoietin is not a viable human therapeutic product; human recombinant erythropoietin, on the other hand, has been proven to be clinically effective, *and* is the first therapeutic product which can be used to effectively treat the hundreds of thousands of patients who suffer from anemia and other disorders involving low blood counts.

App. No. 113,178, *Amendment under Rule 16* at 4, June 5, 1989 (emphasis in original).

The record in the district court contains evidence, presented by persons experienced in this field of science, that the limitation to "a therapeutically effective amount" distinguishes the genetically engineered EPO from known EPO isolates. The district court construed the claims from the viewpoint of the skilled artisan, upon reading and understanding the specification and the restrictions flowing from the prosecution history. My concern about this court's

methodology is that the panel majority does not apply these standard tools of claim construction. The court's holding that "a therapeutically effective amount" includes any amount of EPO that exhibits a physiologic effect, whether or not the amount of EPO is adequate to provide therapy for any disorder, imparts to the claims the scope that was excluded during prosecution.

Although this court has urged caution in construing claims in order to preserve their validity, no precedent or logic requires that when more than one claim construction is available, the court must choose the broader one although it may invalidate the claim. *See Phillips*, 415 F.3d at 1327 (court may not construe claims as would be appropriate to preserve their validity unless "after applying all the available tools of claim construction . . . the claim is still ambiguous"); *see also Smith v. Snow*, 294 U.S. 1, 14 (1935) ("if the claim were fairly susceptible to two constructions, that should be adopted which will secure to the patentee his actual invention"); *Modine Mfg. Co. v. United States Int'l Trade Comm'n*, 75 F.3d 1545, 1556 (Fed. Cir. 1996) ("When claims are amenable to more than one construction, they should when reasonably possible be interpreted so as to preserve their validity.").

Here, the specification and prosecution history make clear that the claimed invention is the "therapeutically effective amount" of engineered recombinant EPO. As was explained to the patent examiner and again in the district court, the prior art isolates of EPO were ineffective to heal or cure. Just as the prosecution record cannot enlarge the claims beyond what the inventor has presented as his invention, so the court cannot enlarge the claims beyond the limitations imposed by the patentee. *See Phillips*, 415 F.3d at 1319 (rejecting definitions broader than the technical usage specific to the invention). The court in this case has departed from these fundamental principles. We should speak *en banc* to clarify that it is

appropriate, and necessary, to look at what has in fact been invented, prosecuted, and patented, and construe the claims accordingly.

II

I do not share the view, expressed here by some colleagues, that this court should not intrude upon panel decisions when major errors of claim construction are pointed out on petition for rehearing *en banc*. The Federal Circuit has a special obligation to provide predictability and consistency in patent adjudication, for our panel decisions are of nationwide effect; indeed, this obligation was a justification for the court's holding, a decade ago, that the district court's claim construction receives non-deferential review on appeal. This appellate position imposes on us the obligation to state the correct law, even on rehearing *en banc*. If the meaning of "therapeutically effective amount" is treated as a question of law, its correct definition as well as the methodology by which it is defined are squarely within the criteria for rehearing *en banc*. And if the meaning is recognized as a case-specific finding of fact, appellate review warrants deference to the trier of fact, a deference here lacking.

III

I continue to believe that findings of science/technology-based facts in patent cases should receive appellate review on the same basis as other science-based findings, guided by *Daubert* and the Court's ensuing elaborations. The Court's and our own precedent require the trial judge to evaluate scientific evidence and expertise from the viewpoint of a person experienced in the field of science, a framework that aptly fits evaluation of the technologic content and scope of patents, an analysis whose intermingling of fact and law is well served by the procedures and the adjudicatory skill of the district courts. The Federal Circuit's position that patent interpretation requires more rigorous appellate review than other fact/law issues has not well withstood the test of

experience. It is time to reopen the question and to rethink, *en banc*, the optimum approach to accuracy, consistency, and predictability in the resolution of patent disputes, with due attention to judicial structure, litigants' needs, and the national interest in invention and innovation.

LOURIE, *Circuit Judge* concurring.

I concur in the decision of the court not to rehear this case en banc. I do so, even though I agree that the panel erred in construing the claim limitation "a therapeutically effective amount." In my view, the panel dissent by Chief Judge Michel was correct, as was the decision by the district court and the current dissent by Judge Newman. However, I do not believe that every error by a panel is enbancable. A panel is entitled to err without the full court descending upon it.

Federal Rule of Appellate Procedure 35(a) provides that "[a]n en banc hearing or rehearing is not favored and ordinarily will not be ordered unless: (1) en banc consideration is necessary to secure or maintain uniformity of the court's decisions; or (2) the proceeding involves a question of exceptional importance." Our Internal Operating Procedures ("IOPs") state that "[a]mong the reasons for en banc actions are: (1) necessity of securing or maintaining uniformity of decision; (2) involvement of a question of exceptional importance; (3) necessity of overruling a prior holding of this or a predecessor court expressed in an opinion having precedential status; or (4) the initiation, continuation, or resolution of a conflict with another circuit." IOP 13(2).

This issue is thus enbancable only on the uniformity or exceptional importance grounds. However, the interpretation of "a therapeutically effective amount" with respect to this particular patent specification seems to me to be case-specific, and it does not therefore raise a question of uniformity of decision or exceptional importance. The term, while in my view incorrectly construed by the majority of the panel, does not necessarily apply to specifications of other patents. In addition, while the result may be of exceptional importance to the parties, it does not seem to be so to the law.

I therefore concur in the decision of the court not to rehear the case en banc, although I disagree with the majority's holding.

RADER, *Circuit Judge*, dissenting from denial of the petition for rehearing en banc.

I agree with the reasoning of Chief Judge Michel's and Judge Newman's dissents. Like them, I urge this court to accord deference to the factual components of the lower court's claim construction. Under current law, this court accords no deference whatsoever to a district court's claim construction. *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1451, 1455-56 (Fed. Cir. 1998) ("[C]laim construction, as a purely legal issue, is subject to de novo review on appeal."). The Supreme Court recognized that, far from a "purely legal issue," claim construction "falls somewhere between a pristine legal standard and a simple historical fact." *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 388 (1996).

Quoting the Supreme Court, this court agreed with the Supreme Court's recognition that "the fact/law distinction at times has turned on a determination that, as a matter of sound administration of justice, one judicial actor is better positioned than another to decide the issue in question." *Cybor*, 138 F.3d at 1455. In this case, the district court's analysis of "therapeutically effective amount" deserved greater deference. As is often the case, the district court was better positioned than this court to reach the proper construction. After all the district court has more tools, more time, and more direct contact with factual evidence than this appellate body. *Id.* at 1477 (Rader, J., dissenting) ("Trial judges can spend hundreds of hours reading and rereading all kinds of source material, receiving tutorials on technology from leading scientists, formally questioning technical experts and testing their understanding against that of various experts, examining on site the operation of the principles of the claimed invention, and deliberating over the meaning of the claim language. If district judges are not satisfied with the proofs proffered by the parties, they are not bound to a prepared record but may compel additional presentations or

even employ their own court-appointed expert."). Indeed, in this case, the trial court held a nine-day trial, including testimony of artisans informed of the meaning of "therapeutically effective amount" at the time of invention. The trial court, while noting that it did not rely on expert testimony to construe the claim, specifically noted that such testimony offered during the trial fully supported the district court's claim construction. Given this court's rule toward limited reliance on extrinsic evidence in claim construction, *Forest Labs., Inc. v. Abbott Labs.*, 239 F.3d 1305, 1311 (Fed. Cir. 2001) (citing *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1584 (Fed. Cir. 1996)), district court judges have learned to disclaim any reliance on expert testimony. Yet, in this case the trial court took testimony for nine days – hardly necessary if the judge was merely reading and relying upon the intrinsic patent document alone.

The district court's construction of "therapeutically effective amount" also falls in line with prior opinions of this court and suggests that artisans in this field would accord the term its customary usage. *Geneva Pharm. v. GlaxoSmithKline*, 349 F.3d 1373, 1383 (Fed. Cir. 2003) (finding that "effective amount" is a common and generally acceptable term for pharmaceutical claims and is not ambiguous or indefinite); *Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 344 F.3d 1274, 1278 (Fed. Cir. 2003) (Because the patentee did not deviate from the accustomed meaning of the disputed claim term, the term "effective amount" is construed in view of its ordinary and customary meaning). Thus, I would grant en banc review.

GAJARSA, LINN and DYK, *Circuit Judges*, concurring in the denial of the petition for rehearing en banc.

We concur in the denial of rehearing en banc. Our concurrence should not be read as an endorsement of the panel's claim construction in this particular case, nor as an unqualified endorsement of the en banc decision in *Cybor Corp v. FAS Techs., Inc.*, 138 F.3d 1448 (Fed. Cir. 1998). In an appropriate case we would be willing to reconsider limited aspects of the *Cybor* decision. In our view an appropriate case would be the atypical case in which the language of the claims, the written description, and the prosecution history on their face did not resolve the question of claim interpretation, and the district court found it necessary to resolve conflicting expert evidence to interpret particular claim terms in the field of the art. This is not such a case.

In this case the district court explicitly and repeatedly disavowed reliance on extrinsic expert evidence in construing the claim term "therapeutically effective." The district court noted that "[d]emonstrative exhibits were presented and references were made to certain expert testimony, but extrinsic evidence was not admitted." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 339 F. Supp. 2d 202, 222 (D. Mass. 2004). Ultimately, the district court concluded:

> While the expert testimony does support the plain and ordinary meaning of the term since it defines what 'cure' means in the context of anemia patients, the Court will not rely on it to construe the claim, because even the *Altiris [Inc. v. Symantex Corp.*, 318 F.3d 1363 (Fed. Cir. 2003)] court made clear that it was looking to expert testimony merely to understand the technology—not to construe the term itself.

Amgen, 339 F. Supp. 2d at 230 n.27; *see id.* at 233 n.29 (noting that extrinsic evidence was not being used "to define the term").[1]

The district court proceeded to construe the claim "therapeutically effective" without resort to extrinsic expert evidence. It first "look[ed] to the plain and ordinary meaning of the words of the patent claim," *id.* at 229, then "review[ed] the specification to determine whether the patentee has used terms in a manner inconsistent with the ordinary meaning or has become his own lexicographer," *id.* at 232, and finally "consider[ed] the prosecution history to determine whether the applicant ha[d] made any express representations regarding the claim's scope," *id.* at 238. No deference is due a district court's legal interpretation of the claim language, written description, and prosecution history that an appellate court is equally competent to interpret.

Since the district court did not rest its interpretation on factual findings concerning conflicting expert evidence and neither the panel majority nor the dissent addressed this issue, we do not believe that this is the appropriate case in which to reconsider aspects of the *Cybor* decision.

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[1] *See also id.* at 226 (noting that expert testimony "is extrinsic evidence to which resort ought to be had only 'if necessary'"); id. at 231 n.28 ("[T]he Court cannot rely on expert testimony to help construe the term 'therapeutically effective' unless absolutely necessary.")

MOORE, *Circuit Judge*, dissenting from the denial of the petition for rehearing en banc.

I dissent from this court's denial of the petition for rehearing en banc. First, let me begin by saying that under the court's present standard of de novo review, in my opinion the district court's construction of "a therapeutically effective amount" was correct. I need not articulate all the reasons that the claims, specification, prosecution history, and extrinsic evidence all support the interpretation given by the district court—the district court's own opinion and the panel dissent by Chief Judge Michel effectively do so. If the only issue were one of case-specific mistake, I would concur in the decision not to hear the case en banc. Federal Rule of Appellate Procedure 35(a) and our Internal Operating Procedures limit the use of en banc.

I dissent because I believe this court should have taken this case en banc to reconsider its position on deference to district court claim construction articulated in *Cybor Corp. v. FAS Tech., Inc.*, 138 F.3d 1448, 1454-55 (Fed. Cir. 1998) (holding that claim construction was purely a matter of law and therefore subject to de novo review). Five judges of this court have written opinions in this case expressing disagreement with the two judge panel majority's claim construction even under the de novo standard of review.

In this case, the district court construed the term "a therapeutically effective amount" with the assistance of a technical advisor (an MIT Professor) and a Special Master. The district court opinion explains that the term was construed using the patent claims, the specification, the prosecution history, three different dictionaries, and prior art.[1]

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[1] Dictionaries, technical treatises, and prior art disclosures are extrinsic evidence relied upon by the district court to construe this term. *See Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 339 F. Supp.2d 202, 226-228 (D. Mass. 2004) (detailing the dictionary definitions); *Id.* at 244 n.46 (explaining that the prior art disclosed to the patent examiner also

The opinion also explains that the claim construction is supported by the expert testimony presented by the parties in this case,[2] but then disavows using it to "define the term" or "construe the term" instead stating that it is being used to "understand the technology."[3]

I commend the district court for its thorough, detailed, thoughtful, and competent efforts in construing this claim limitation. The district court did everything we have asked it to do, and in my opinion, did it correctly. While this may not be a basis for taking the case en banc, reconsideration of the deference accorded to the district court in this case would have been. Therefore, I would grant en banc review.

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supports the district court's interpretation). When the district court disavows use of extrinsic evidence, it seems to be focusing on expert testimony.

[2] *Id.* at 244-45 n.47 (finding that "two crucial witnesses for the defense conceded" points which support the district court's claim construction).

[3] The district court goes on to point out that the Federal Circuit precedent has created a "conundrum" by: "discouraging resort to extrinsic evidence while at the same time urging courts to begin claim construction by considering the plain and customary meaning of a term as understood by one skilled in the art." *Id.* at 226 n.23.